DISEASES of the CHEST

VOLUME XXXVII APRIL, 1960 NUMBER 4

Current Therapy in Pulmonary Tuberculosis

A STUDY OF 10 CASES BY 100 PARTICIPATING PHYSICIANS WITH ANALYSIS OF THEIR OPINIONS

A Report of the Committee on Non-Surgical and Drug Therapy
American College of Chest Physicians

This study is the third of a series designed to obtain current thinking on the treatment of the various types of pulmonary lesions. Ten cases illustrative of the various types of pulmonary tuberculous lesions are presented. Each case with a brief history and a reproduction of the chest x-ray film, was sent to 100 physicians who were selected by the committee because of their wide experience and high qualifications. The same 10 cases were sent to 57 physicians in 1948 and to 100 physicians in 1953 for the same purpose and results were published in DISEASES OF THE CHEST.

Minimal Cases

Case 1: Minimal right apical lesion.

This 18-year-old white man was found to have a small mottled lesion in his right upper lung field on routine chest x-ray film during examination. He feels perfectly well and has no symptom. Physical examination negative. Intradermal tuberculin milligram of 0.01 OT. positive. Gastric lavage with guinea pig inoculation positive.

Case 3: Minimal pulmonary tuberculosis bilateral, productive, with effusion in the right pleural space.

This 43-year-old white housewife and former nurse noted the onset of easy fatigability and occasional pain in the right side of her chest in May. These symptoms

SUMMARY TABULATION

Type of Therapy	Minimal — Cases 1 and 3			
	1958 — 200 Answers		1953 — 200 Answers	
	No.	Per cent	No.	Per cent
Collapse therapy, plus drugs				
Pneumoperitoneum	4	2	23	11.5
Pneumothorax	0	0	8	4
Phrenic	0	0	3	1.5
Total collapse	4	2	34	17
Surgery, plus drugs				
Excision	31	15.5	9	4.5
Thoracoplasty	0	0	3	1.5
Unspecified	3	1.5		
Total surgery	34	17	12	6

persisted and in September she began to have night sweats. On October 11, she developed acute pain in the right side of her chest, dyspnea, chills and fever to 104° F. Chest x-ray film revealed a homogeneous density in the right pleural space (pleural effusion) and infiltration of both apices — more marked on the right side. Clear yellow fluid was aspirated from the right pleural space which was negative on guinea pig inoculation but material obtained on gastric lavage was positive for tubercle bacilli.

Far Advanced Cases

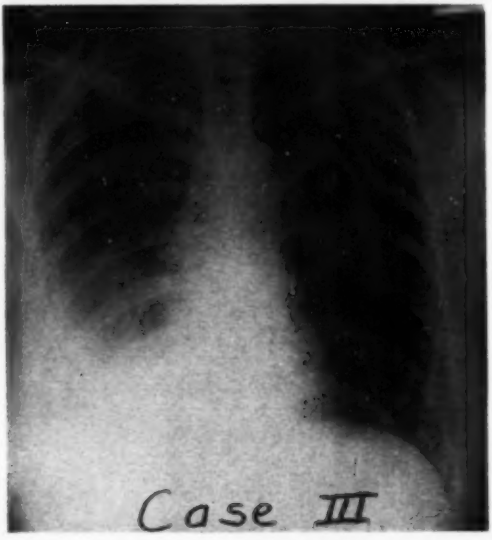
Case 2: Far advanced tuberculous pneumonia.

This 31-year-old white married woman developed acute upper respiratory infection in January, followed by productive cough and fever. She had hemoptysis and then visited her physician. Past history revealed a negative chest x-ray film three years previously. Another film in May of the preceding year was said to show a "spot" on her lung. For the past three to four years, she had noted weakness and easy fatigability, which she attributed to excessive menstrual flow.

Chest x-ray film shows a diffuse homogeneous density occupying the upper half of the right lung field, containing a cavity. Sputum was positive on smear for tubercle bacilli.

Case 6: Far advanced pulmonary tuberculosis, bilateral cavities, acute, with probable tuberculous tracheobronchitis.

This 29-year-old white married woman has been underweight and easily fatigued since childhood. Seven years ago she had an upper respiratory infection and lost from 95 to 75 pounds. She was then fluoroscoped and told that she had tuberculosis, but after six weeks she returned to work, without treatment. In June and again in September, preceding her present illness, she had pleurisy on the left side and was treated

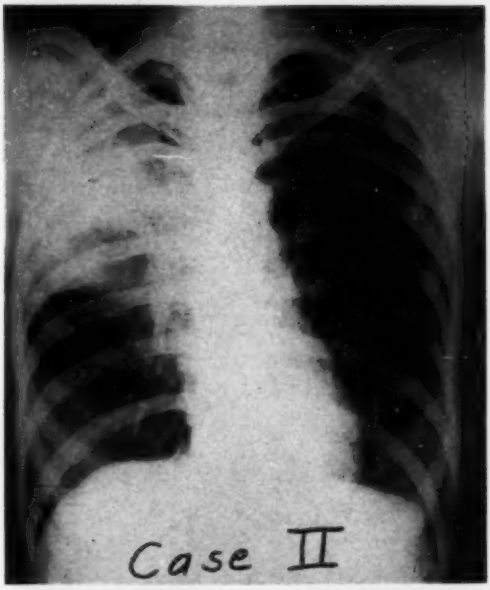


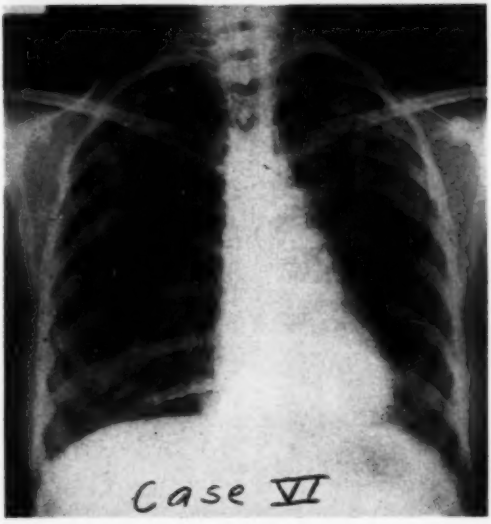
with bed rest and sulfa drugs, only until the pain and fever subsided. Now in February a third attack of pleurisy brought her to another physician. Her tuberculin test, which was said to be negative several times before, was now positive.

Chest x-ray film at this time shows several scattered hard densitities in both upper lung fields. In addition, there is a soft mottled infiltration at the apex of the right lung with a 1 cm. cavity in the right second anterior interspace. There is a more diffuse mottled infiltration in the upper third of the left lung field with a 3 cm. cavity at the level of the left second anterior rib. Sputum was positive for tubercle bacilli.

Case 7: Far advanced bilateral pulmonary tuberculosis, with mottling throughout right lung and large cavity in the left hilum.

This 28-year-old colored married woman had frequent "colds" and an almost continuous productive cough since an attack of pneumonia in September, 18 months ago. On February 6 a chest x-ray film revealed a mottled infiltration of miliary type



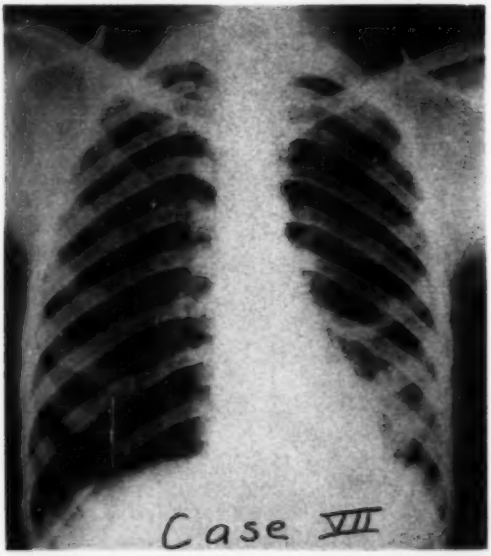


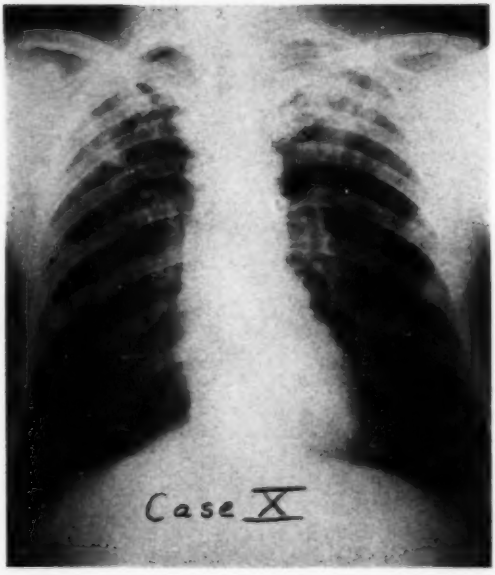
throughout the entire right lung and a 4 cm. hilar cavity with an area of infiltration extending along the border of the cardiac shadow toward the base on the left. Sputum was positive for tubercle bacilli.

Case 10: Far advanced pulmonary tuberculosis, fibrocaseous lesions in the upper half of both lungs with cavity on the left side.

This 57-year-old white American is a sales manager. He had pneumonia at the age of 14, and again at the age of 21.

Present Illness: Two years ago, he began to feel below par. Prostatitis was diagnosed and treated. Last year "heart trouble" was diagnosed. X-ray film of his chest finally taken, shows calcified lesions at the right apex, multiple scattered nodules, little fibrosis, but soft infiltration throughout the upper two-thirds of his right lung.





SUMMARY TABULATION

Type of Therapy	Far Advanced — Cases 2, 6, 7, 10			
	1958 — 400 Answers		1953 — 400 Answers	
	No.	Per cent	No.	Per cent
Collapse therapy, plus drugs				
Pneumoperitoneum	81	20	209	52
Pneumothorax	9	2.4	15	4
Phrenic	0	0	1	0.3
Extrapleural pnx., oleothorax	1	.3	5	1.2
Total collapse	92	23	230	57.5
Surgery, plus drugs				
Excision	240	60	82	20.5
Thoracoplasty	17	4	10	2.5
Unspecified	12	3		
Other types of surgery	4	1		
Total surgery	273	68.3	92	23

The left lung shows a soft mottling throughout the upper one-third with a 1.5 cm. cavity at the level of the first interspace. Sputum was positive for tubercle bacilli. He had very few chest symptoms. No other medical problem.

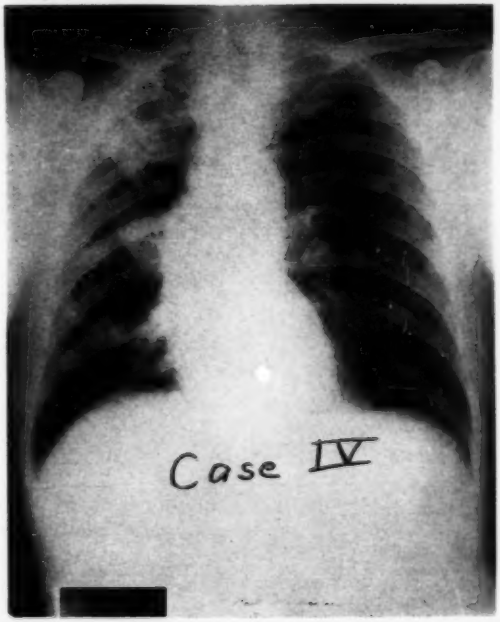
Moderately Advanced Cases

Case 4: Moderately advanced pulmonary tuberculosis; unilateral, no cavity, acute.

This 63-year-old white man noted a productive cough, hoarseness and general run-down feeling in May. Physical examination revealed rales at apex of his right lung and over the right base posteriorly. Chest x-ray film shows an area of infiltration at the periphery of the right upper lung field, a wedgeshaped area of increased density at the right hilus and a small patchy infiltration at the right base. Sputum was positive for tubercle bacilli.

Case 5: Moderately advanced pulmonary tuberculosis, unilateral, no cavity, fibrotic.

This 48-year-old white man had intermittent chest pain on the left since June one year ago. The following April he developed considerable epigastric distress and lost 10 to 15 pounds over the next few months. In October his x-ray film revealed a diffuse fine mottling throughout the upper half of the right lung field. Tuberculin test was positive and sputum was positive for tubercle bacilli. Excellent general condition. No other symptoms but a mild morning, slightly productive cough.



SUMMARY TABULATION

Type of Therapy	Moderately Advanced Cases — 4, 5, 8, 9			
	1958 — 400 Answers		1953 — 400 Answers	
	No.	Per cent	No.	Per cent
Collapse therapy, plus drugs				
Pneumoperitoneum	38	9.5	115	29
Pneumothorax	5	1.3	33	8
Phrenic	0	0	0	0
Extrapleural pnx., oleothorax	0	0	2	0.5
Total collapse	43	10.8	150	37.5
Surgery, plus drugs				
Excision	133	33.2	79	19.5
Thoracoplasty	7	1.8	16	4
Unspecified	14	3.5		
Other types of surgery	4	1		
Total surgery	158	39.5	95	23.5

Case 8: Moderately advanced pulmonary tuberculosis with cavity at right apex.

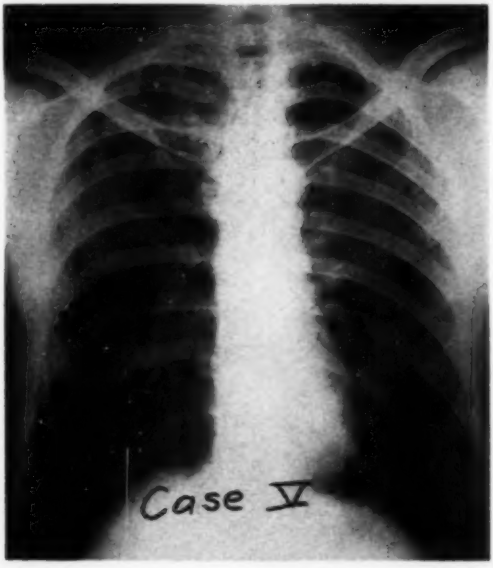
This 34-year-old man had occasional bilateral chest pains for four years when, following an appendectomy in January, he developed an ischiorectal abscess. On July 31, he was rejected by the army because of a "tuberculous cavity" in the right upper lung. On August 18, he had a small hemoptysis followed by fever for several days. He visited a physician, and physical examination plus chest x-ray film revealed only a cavity at the right apex. Sputum was positive for tubercle bacilli.

Case 9: Moderately advanced pulmonary tuberculosis, acute, more extensive on the left.

This 34-year-old white married woman felt well until she developed pain beneath the left scapula. Her physician found she reacted to tuberculin (0.01 mg. OT). A chest x-ray film revealed a soft mottled infiltration in both upper lung fields, more extensive on the left. Sputum was positive for tubercle bacilli.

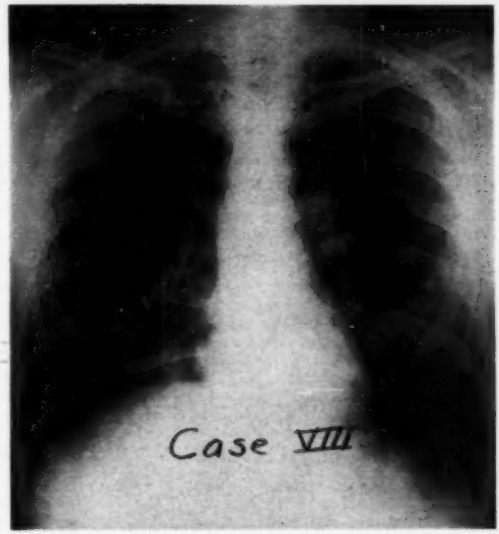
Summary of Opinion Expressed

All of the 100 participating physicians answered that they would use chemotherapy immediately upon diagnosis in addition to bed rest. This was not the case in the previous studies. The drugs of choice were isonicotinic acid hydrazide (INH), para-

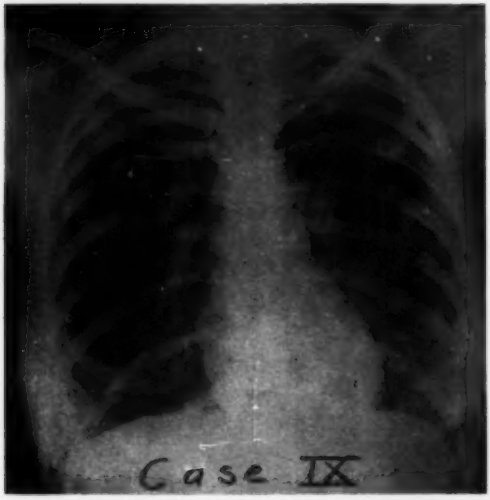


SUMMARY TABULATION

Type of Therapy	Total — 1958		Total — 1953	
	1000 Answers		1000 Answers	
	No.	Per cent	No.	Per cent
Collapse therapy, plus drug				
Pneumoperitoneum	123	12.3	347	34.7
Pneumothorax	14	1.4	56	5.6
Phrenic	0	0	4	0.4
Extrapleural pnx., oleothorax	1	0.1	7	0.7
Unspecified	1	0.1		
Total collapse	139	13.9	414	41.4
Surgery, plus drugs				
Excision	404	40.4	170	17
Thoracoplasty	24	2.4	29	2.9
Other procedures	8	0.8		
Total surgery	436	43.6	199	19.9



aminosalicylic acid (PAS) and streptomycin (SM). Whereas 10 years ago SM was used solely by as large a group as 44 per cent, combined therapy was the exclusive choice in the 1958 study, as well as in 1953. However, SM was no longer one of the favored drugs in double therapy in 1958. A change to the double combination of INH and PAS was noted in this study, and many expressed a preference for this combination as a routine choice. Not only was this INH—PAS combination used routinely but also the dosage of 300 mg. of INH and 12 Gm. of PAS in divided doses daily was considered standard by many. Those who did not recommend a standard dose of INH and PAS usually expressed a preference for higher dosages of INH in the double combination. When this occurred, addition of pyridoxine was recommended. It was also observed that there was an increasing tendency to use triple drug therapy as compared to the study made five years ago. Where SM was used, agreement as to method of administration was not general, but recommendations for 1 Gm. daily during the acute period and thereafter two times weekly seemed popular. In cases of drug failure, there were a few suggestions to change to pyrazinamide, Viomycin or Serocycline. In acute febrile cases, a small number suggested the addition of corticosteroids during the period of high fever and acute symptoms. The duration of drug therapy was also extended. A minimum of 24 months was suggested by most and an even longer period (three to five years) by a sizeable number. This was in marked contrast to the 1953 study where 12 months of combined drug therapy was popular and where only a few expressed a desire for as much as 24 months of therapy. A definite trend by a small percentage to prolong therapy for life by continuing with INH after the period of combined therapy was noted.



Non-surgical collapse therapy seems to have become a much less popular procedure. The number recommending this type of treatment was considerably smaller than that of 1953. Where such procedure was recommended, pneumoperitoneum was almost exclusively used. Pneumothorax was rarely recommended. Phrenic operations, extrapleural pneumothorax, and oleothorax have become obsolete. The decreased tendency to use non-surgical collapse therapy appears true for all grades of disease. When collapse therapy was used, the time for initiation varied usually from immediately to three months. There was no general agreement as to the duration of pneumoperitoneum. This was equally true in 1953 — the answers ranged from one to five years.

Surgery appears to have become a much more important and useful weapon in the attack upon active tuberculosis. A much greater number preferred this method of treatment in 1958 as compared to the number in the two previous studies. This was not only true of those cases with extensive disease, but also in the less advanced types and minimal cases. The procedure of choice was excisional surgery. Thoracoplasty has largely fallen into disuse. In a few instances where the disease was extensive and pulmonary function diminished considerably, extraperiosteal lucite plombage was recommended. Decortication was also selected by a few where pleural thickening appeared to exist. The favorite time for initiation of surgery was after six months of chemotherapy and bed rest. Post-surgical bed rest varied up to a period of six months, although a considerable number were willing to shorten this period to merely post-operative care.

The answers to the questions of length of time of complete bed rest varied. This was also true for the duration of sanatorium stay. However, a marked trend to decrease the time of total complete bed rest and of sanatorium stay was noted in comparison to the study of five years ago. This may be explained in part by more intensive chemotherapy, and also by an increased tendency for surgical intervention. A considerable number stated that they believed in modified rest only. In the less extensive cases, a few felt that sanatorium stay was unnecessary and that the patient could be treated at home. The presence of good home conditions was another factor influencing decreased sanatorium stay.

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Contralateral Pneumothorax after Pneumonectomy for Carcinoma

JOHN B. BLALOCK, M.D.*
New Orleans, Louisiana

Fortunately, contralateral pneumothorax occurs rarely after pneumonectomy. This complication was detected during the immediate postoperative period in four of 340 patients having pneumonectomy for carcinoma at the Ochsner Clinic from January 1942 through June 1958. To our knowledge delayed pneumothorax has not occurred in any of the remaining patients. This lends support to the impression that in these cases the pneumothorax is not truly spontaneous but is precipitated by some operative or postoperative condition, which may be apparent or may defy clarification even after reoperation or at necropsy.

The obvious compromise of pulmonary reserve incident to pneumonectomy renders such patients unusually vulnerable to pulmonary complications. For this reason, almost any complication of pneumonectomy may be a major one. The attending physician is constantly aware of the more common complications, such as pulmonary edema, excessive bronchial secretion, atelectasis, pneumonitis, congestive atelectasis, and tension hemopneumothorax of the operative side, whereas this rarer condition may be completely unsuspected. Pneumothorax has been reported as a complication of surgical procedures involving the neck,[1,2] chest,[3-12] subdiaphragmatic region[13] and abdomen.[14] It has also complicated induced pneumothorax,[15-20] and pneumoperitoneum.[16] Such an abnormal accumulation of air gains access to the pleural space by one or both of two ways: 1) through a defect in the respiratory tract or 2) through a defect in some structure in proximity to or in fascial plane continuity with the mediastinum and pleural spaces. There seem to be several possible sources and mechanisms of pneumomediastinum and pneumothorax after pneumonectomy: 1) Development of tension hemopneumothorax on the operated side by rapid accumulation of fluid in the pleural space. This may, at least theoretically, result in "driving" the air into the thoracic wall and mediastinum at sites of pleural disruption. 2) Tension pneumothorax may result from flutter valve type leakage of the sutured bronchial stump. 3) Leakage of the trachea, contralateral bronchus, or pulmonary parenchyma incident to operative injury. 4) Leakage of the contralateral pulmonary parenchyma, either from visceral pleural disruption or from disruption of alveoli within the pulmonary substance with extravasation of air to the surface of the lung, root of the lung, mediastinum, and pleural space. 5) Aspiration of outside air into the anatomic planes of the thoracic wall and mediastinum, either through a defect in the skin or perforation of the esophagus.

Because of the rarity of this complication, the four cases encountered at the Ochsner Clinic will be described in detail.

Report of Cases

CASE 1: A white man, aged 55 years, was seen June 6, 1947, complaining of pain in the left side of the chest, cough, anorexia, loss of weight, and easy fatigability of

*From the Department of Surgery, Ochsner Clinic.

five months' duration. His illness had been attributed to a pulmonary lesion, which had been treated with roentgen rays without apparent benefit. The clinical and roentgenographic evidence was suggestive of broncnogenic carcinoma of the left upper lobe. Bronchoscopic biopsy failed to establish the diagnosis. The clinical impression that the patient could withstand left pneumonectomy was strengthened by the fact that he tolerated induction of left pneumothorax (1700 cc.) without difficulty.

At operation on June 14, 1947, a large carcinoma of the upper lobe of the left lung with extensive metastasis to the mediastinal lymph nodes was encountered. In the course of mediastinal dissection, during mobilization of a large retrotracheal node, the right pleural cavity was entered. The pneumonectomy was completed, after which the defect in the right mediastinal pleura was sutured and reinforced with absorbable gelatin sponge, and the sutured bronchial stump was covered with mediastinal pleura and areolar tissue. The thoracic wall was closed without drainage. Aspiration of the right pleural space yielded a small amount of air.

His condition was satisfactory at the conclusion of the operation, but during the ensuing three hours dyspnea and cyanosis became severe. Thoracentesis on the right side yielded a large amount of air and resulted in considerable improvement. Further respiratory distress occurred after three more hours. A catheter was inserted into the right pleural space. The next morning subcutaneous emphysema in the left side of the chest and both supraclavicular areas was present. Severe mediastinal emphysema and right pneumothorax were demonstrated in a roentgenogram of the chest (Figure 1a). There was no evidence of a fluid level in the left hemithorax. After placement of a second tube in the right pleural space, the pneumothorax was controlled, the interstitial emphysema subsided, and he improved steadily. The right lung was clear and fully expanded by the 10th postoperative day, when he was discharged from the hospital in satisfactory condition (Figure 1b).

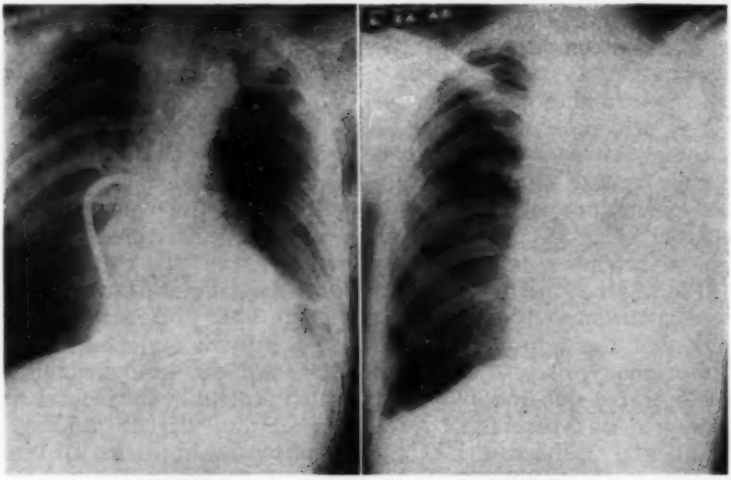

FIGURE 1a FIGURE 1b

FIGURE 1a: *Case 1.* There is residual right pneumothorax after insertion of a single tube. The left hemithorax contains air and extensive interstitial emphysema of the thoracic wall is present. FIGURE 1b: A roentgenogram of the chest on the tenth postoperative day shows complete reexpansion of the right lung, obliteration of the left pleural space by effusion and subsidence of the interstitial emphysema.

Comment: The likelihood that the preoperative left pneumothorax had any relation to the development of interstitial emphysema and right pneumothorax seems to be remote. Opening of the right pleural space during mediastinal dissection resulted in development of right pneumothorax and necessitated use of increased positive pressure anesthesia until the defect was closed. The minimum accumulation of fluid on the operative side militates against the possibility of displacement of the trapped air in the left hemithorax as the source of the right pneumothorax. Furthermore, the need for thoracentesis and catheter drainage, and the severe interstitial emphysema are convincing evidence that there was an active leak from the tracheobronchial tree during the postoperative period. There was nothing in the postoperative course to suggest a fistula from the bronchial stump or an injury to the trachea. The occurrence of interstitial pulmonary emphysema in the right lung would seem to be the most likely cause of the pneumothorax and severe degree of interstitial emphysema.

CASE 2: A white man, 49 years old, had an asymptomatic lesion in the right lung that was detected seven months previously during roentgenography of the chest incident to an examination after an automobile accident. The progress of the lesion was followed by serial roentgenography. In the roentgenogram taken the day before admission the lesion was found to have doubled in size. A peripheral type bronchogenic carcinoma was the presumptive diagnosis; in addition, the patient had clinical evidence of emphysema with increased anteroposterior diameter of the chest and kyphosis. Pulmonary function studies indicated that the patient could withstand a major surgical procedure.

On August 13, 1952, at thoracotomy the diagnosis of bronchogenic carcinoma was confirmed and right pneumonectomy was performed without incident. The immediate postoperative reaction was good. The patient's condition was satisfactory at the time of morning rounds on the first postoperative day. Later that morning signs of respiratory difficulty developed, with cyanosis, dyspnea, and an increase in respiratory rate to 40 per minute. On examination of the chest at this time, the left lung was "clear." Repeated attempts to clear the airway by tracheal suction yielded only small amounts of mucus. The respiratory distress became more and more severe and the patient died in mid-afternoon.

At necropsy the left pleural cavity contained a large amount of air and the left lung was completely collapsed except for a small area in the left apex. Residual tumor was found in one mediastinal node and in one small area in the liver. The lesion in the resected lung proved to be adenocarcinoma with mediastinal node metastasis.

Comment: The first suggestion of respiratory distress appeared almost 24 hours after operation and proved to be due to tension pneumothorax. There was no clinical or postmortem evidence of interstitial emphysema and no bullae were described in the resected lung or in the remaining lung at necropsy. In spite of this, a defect on the surface of the lung would best explain this series of events. Roentgenography of the chest was not performed during the postoperative period.

CASE 3: A man, aged 65 years, complained of hemoptysis of two months' duration. Serial roentgenograms of the chest showed no abnormality until the one taken just before he came to the clinic, in which right hilar enlargement was noted. Roentgenography of the chest at the clinic confirmed this and indicated probable bronchogenic carcinoma. Results of examination of the sputum and bronchoscopic biopsy were not diagnostic. After demonstration of satisfactory pulmonary function, exploratory thoracotomy was performed on April 9, 1956. The histologic diagnosis was epidermoid bronchogenic carcinoma with extensive involvement of the mediastinal nodes.

Immediately after radical right pneumonectomy, hypotension, tachypnea, tachycardia, and extreme restlessness developed. Because the 1500 cc. of blood given during the operation was considered insufficient, an additional 1000 cc. was given. Also, an infusion containing norepinephrine was started. A portable roentgenogram of the chest, made the evening of operation, revealed the right hemithorax to be about 75 per cent opacified by accumulation of intrapleural fluid, and considerable interstitial

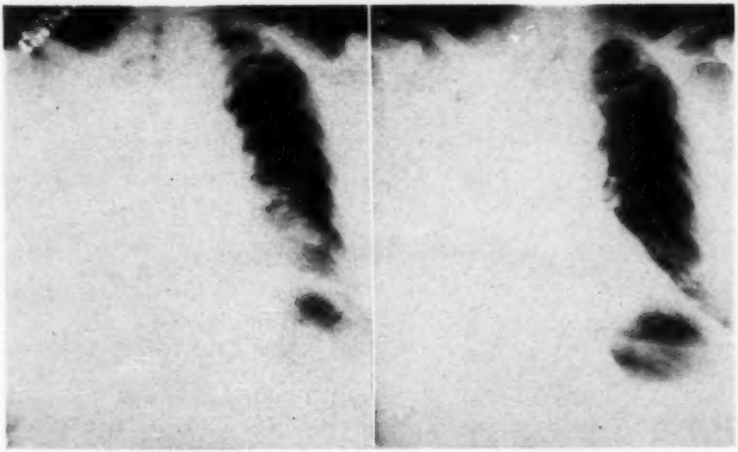

FIGURE 2a FIGURE 2b

FIGURE 2a: *Case 3.* Roentgenogram taken on the first postoperative day shows significant compression of the left lung by pneumothorax and interstitial emphysema of the cervical region. FIGURE 2b: Two days later the left lung has completely re-expanded and the interstitial emphysema is subsiding.

emphysema in both supraclavicular regions and in the right thoracic wall. The left lung appeared to be clear in spite of diminished breath sounds, wheezing and rales at the base and in the lateral thoracic region. At bronchoscopy the tracheobronchial tree contained no significant amount of secretion and the closure of the bronchial stump was intact. An electrocardiogram was similar to the one taken preoperatively. The patient remained in critical condition throughout the night and into the following day, when roentgenography of the chest indicated considerable change (Figure 2a). There was left pneumothorax with shift of the heart and mediastinum to the right in spite of a large amount of fluid in the pleural space. A catheter was inserted into the left pleural space by closed thoracotomy with immediate, almost complete, resolution of the pneumothorax. Thereafter, his condition improved rapidly and by the second postoperative day the left pneumothorax was completely relieved (Figure 2b). Convalescence was satisfactory until the sixth postoperative day, when cardiac and respiratory difficulties suddenly developed. The patient had severe bronchospasm, profuse tracheobronchial secretion, labored respiration and tachycardia. There was no clinical or roentgenographic evidence of bronchial leakage or of collapse of the left lung. He rapidly lapsed into coma and died.

At necropsy atherosclerosis of the coronary arteries with recent thrombosis of the right coronary artery, early bronchopneumonia secondary to aspiration, and partial congestive atelectasis of the left lung was found. The bronchial stump was intact; no pneumothorax or residual tumor was demonstrated.

Comment: The extensive interstitial emphysema and pneumothorax suggest an active leak from the respiratory tree rather than passive displacement of trapped air from the opposite side. The thrombotic change in the diseased coronary vessel was most probably precipitated by the state of shock during the immediate postoperative period.

CASE 4: A white farmer, aged 48 years, came to the clinic on May 3, 1956, for evaluation of an illness that began with pleuritic pain in the left side of the chest and hemoptysis three years earlier. There had been repeated clinical and roentgenographic evidence of disease of the left lower lobe of the lung. A trial of antituberculous therapy had been ineffective.

After establishment of a diagnosis of bronchogenic carcinoma of the left lower lobe by bronchoscopy and demonstration of satisfactory pulmonary function to withstand pneumonectomy, thoracotomy was performed on May 9, 1956. Palliative radical pneumonectomy was performed, since the tumor had metastasized to the hilar and mediastinal lymph nodes.

The postoperative course was satisfactory. The right lung was considered normal on clinical examination, although he thought he had slight difficulty in breathing. Roentgenography of the chest was performed on the fifth postoperative day (Figure 3a). There was an estimated 25 per cent collapse of the right lung by pneumothorax with shift of the heart and mediastinum to the left, although the left pleural space

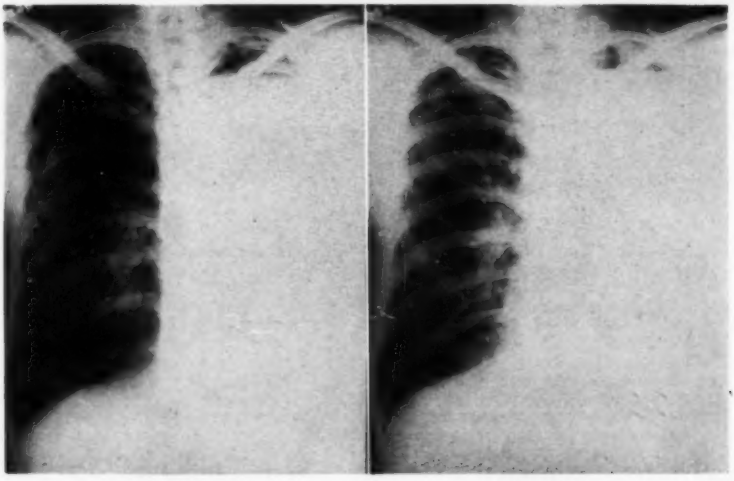

FIGURE 3a FIGURE 3b

FIGURE 3a: *Case 4.* Roentgenogram taken on the fifth postoperative day shows estimated 25 per cent collapse of the right lung. There is no interstitial emphysema and the mediastinum is shifted toward the operative side. FIGURE 3b: Two days after aspiration of 450 cc. of air from the right pleural space only a thin rim of air remains over the apex and the right border of the mediastinum is evident.

was almost completely filled with fluid. The dyspnea was relieved by thoracentesis with removal of 450 cc. of air from the right pleural space. Roentgenography of the chest 48 hours later showed only a thin rim of air over the right apical region (Figure 3b). He was discharged on the ninth postoperative day.

Comment: A small amount of crepitation is sometimes detected about the operative wound during the first few days after pneumonectomy. The usual explanation for this is the development of some degree of tension in the residual air in the hemithorax from which the lung has been removed, with extravasation of air into the tissues adjacent to the wound. The roentgenogram of the chest made on the fifth postoperative day demonstrated, in addition to the mild, right pneumothorax, that the left pleural space had already been almost obliterated by accumulation of fluid. Although the opposite pleural space had not been grossly opened, the nodal dissection incident to radical pneumonectomy certainly exposed the opposite pleura at multiple sites. Perhaps the strongest objections to displacement of trapped air from the operative side as a possible explanation for this mild degree of pneumothorax are: 1) the mediastinum was shifted toward rather than away from the operative side, and 2) the fact that one frequently sees the hemithorax fill with fluid in a short time and one rarely sees contralateral pneumothorax.

Discussion

Ten cases of contralateral pneumothorax in the immediate period after pneumonectomy have been found in the medical literature.[3,6,7,9,11] A ruptured bleb or bulla was demonstrated in 6 of these 10 cases[6,9,10] and was suggested as the probable cause in three of the remaining four cases.[7,11] In the other case it was thought that there had possibly been a communication through the mediastinum, but such a defect was not demonstrated at necropsy.[6] One case of contralateral pneumothorax that occurred 60 days after pneumonectomy was reported by Melick and Gutekunst.[4] Only two of these 11 patients survived.[4,9]

Persistence of the leakage in Cases 1 and 3 and the high degree of tension in Case 2 must undoubtedly be attributed to an active leak in the respiratory tree. The extensive supraclavicular and thoracic wall interstitial emphysema in Cases 1 and 3 are more in keeping with disruption within the pulmonary parenchyma, whereas the pneumothorax without interstitial extravasation in Cases 2 and 4 could be explained by a defect on the surface of the lung. No evidence of leakage at the suture line of the bronchial stump or of injury to the structure of the major airway was demonstrated in the two cases in which necropsy was performed, nor could such leakage be suspected by the subsequent course of the two surviving patients. Therefore, it seems most probable that the leak occurred at the parenchymal level. A ruptured bulla would be the most direct and easily understood mechanism of this occurrence. However, there was no mention of evidence of bullae in any of the four lungs removed at operation or of the two examined at necropsy. The other surface abnormality, the subpleural bleb, is the surface evidence of interstitial pulmonary emphysema so convincingly substantiated by the work of Macklin and Macklin.[12] This concept is strengthened by Dickie's[10] study of cases of spontaneous pneumothorax. The bleb is evidence that some disruption in the lining of the respiratory parenchyma has occurred and that the extravasation of air occurs medially to the mediastinal pleura as well as peripherally to the visceral pleura. Further, Macklin and Macklin showed that once a site of leakage has developed, the leak can be maintained by considerably lower pressure than was necessary to produce the original disruption. It has been shown that lungs confined to their normal volume can withstand a considerably higher intrapulmonary pressure before leakage occurs than can a lung which can be distended beyond its optimum volume.[20] Some degree of at least intermittent overexpansion of the opposite lung must occur in virtually every open thoracotomy provided the mediastinum is mobile.

The cases of pneumothorax herein presented can hardly be considered as "spontaneous" but rather seem to be in some way precipitated by conditions existing within the pulmonary tissue during or after pulmonary operations. Furthermore, these conditions seem to result from altered pulmonary mechanics associated with these types of operations, as pneumothorax attributed to this mechanism, that is, interstitial pulmonary emphysema incident to extrathoracic operations, appears to be extremely rare.

Macklin[21] suggested that a local area of tension might be built up beyond a bronchial plug producing a ball-valve effect. Such a local mechanism could occur while normal pressure conditions existed in the major portion of the pulmonary system and could explain the occurrence of pneumothorax with the subject at complete rest. In view of the wide range of variations in pressure and some variations in volume to which the lung is subjected during and after operation, and considering the great number of thoracotomies that have been performed, one wonders at the rarity of this complication. The operative and postoperative courses of patients undergoing pulmonary resection are so remarkably similar that from one patient to the next it is difficult or impossible to single out any variation in these patients to account for this rare complication. In the absence of a gross site of leakage one seems forced to attribute this complication to disruption of the pulmonary parenchyma. In the presence of a mobile mediastinum in cases of open thoracotomy the contralateral lung is fre-

quently distended beyond its optimum volume. Such overexpansion at normal or increased intrapulmonary pressure would seem to be a likely explanation for parenchymal disruption.

SUMMARY

Contralateral pneumothorax is one of the rarer complications of pneumonectomy. Four such cases among 340 pneumonectomies for carcinoma at the Ochsner Clinic and 11 cases found in the literature indicate that this complication in itself should be completely correctable in most instances if recognized promptly and the pneumothorax relieved. The source of the pneumothorax is most probably a pulmonary parenchymal disruption, either within the pulmonary substance or on the surface of the lung.

RESUMEN

El neumotórax contralateral es una de las más raras complicaciones de la neumonectomía. En la clínica Oschner entre 340 neumonectomías por carcinoma, se encontraron cuatro casos y 11 más en la literatura, indican que esta complicación debe ser completamente corregible en la mayoría de los casos si se reconoce prontamente y se trata el neumotórax.

La cause del neumotórax es lo más probable una ruptura del parénquima pulmonar ya sea dentro de la masa pulmonar o en la superficie.

RESUMÉ

Le pneumothorax controlatéral est une des plus rares complications de la pneumonectomie. Quatre cas de ce type sur 340 pneumonectomies pour cancer à la Clinique Ochsner, et II cas trouvés dans la littérature montrent que cette complication devrait être en elle-même complètement curable dans la plupart des cas si elle est reconnue rapidement et si on supprime le pneumothorax. L'origine du pneumothorax est le plus vraisemblabement une rupture parenchymateuse pulmonaire soit dans la profondeur du parenchyme pulmonaire soit à la surface du poumon.

ZUSAMMENFASSUNG

Der kontralaterale Pneumothorax ist eine der selteneren Komplikationen der Pneumonektomie. Vier solcher Fälle unter 340 Pneumonektomien wegen Carzinom an der Ochsner-Klinik und 11 in der Literatur gefundene Fälle erweisen, dass sich diese Komplikation in den meisten Fällen komplett beheben lassen muss, wenn sie rechtzeitig erkannt und der Pneumothorax beseitigt wird.

Die Herkunft des Pneumothorax ist höchstwahrscheinlich ein pulmonaler Parenchymriss, entweder im Lungeninneren oder an ihrer Oberfläche.

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Cycloserine-Isoniazid in the Treatment of Chronic, Resistant Pulmonary Tuberculosis*

HYO KEUN LEE, M.D., F.C.C.P.
Burkeville, Virginia

Introduction

This report concerns the clinical results observed in patients with chronic pulmonary tuberculosis in whom long-term chemotherapy had failed, who were then treated with cycloserine (CS) and isoniazid (INH). Observations were made with respect to clinical improvement, bacteriological conversion, roentgenographic improvement, closure of cavities and drug toxicity.

Material

Forty-six consecutive patients fitting the following criteria were selected: all patients had received long-term prior chemotherapy and represented failure of treatment with various combinations of SM, PAS, INH; all patients had a positive sputum; all patients were resistant to SM, PAS and INH, either in the laboratory, or clinically, or both.

All patients were Negroes, 22 males and 24 females. The age varied between 17 and 65 years. Forty-one patients were far advanced, 5 were moderately advanced. Thirty-one patients had cavitary lesions.

Four patients had previous chemotherapy with various combinations of SM, PAS, INH less than a year, 20 patients for one to two years, 22 patients for over three years. Three were sensitive to INH (5 mcg./ml.), 5 were partially resistant and 38 were highly resistant at the beginning of CS-INH therapy.

Twenty-nine patients have been treated with 750 mgs. of CS and 300 mgs. of INH per day in divided doses, 17 patients with 500 mgs. of CS and 300 mgs. of INH.

Eleven patients have been observed less than three months, six patients between four and six months, eleven patients between seven and nine months, twelve patients between ten and twelve months, six patients have been studied for more than one year.

Observations

Clinical Improvement: Symptomatic improvement was prompt and marked in most of these cases. Five patients were febrile prior to therapy with temperature ranging from 99° to 102° F. Defervescence was completed by two months in all cases. Thirty patients, or 65 per cent, gained weight: 16 patients 3 to 10 lbs.; 7 patients 11 to 20 lbs.; 4 patients 21 to 30 lbs.; and 3 patients over 31 lbs., the maximum weight gained being 69 pounds. The gain in weight occurred chiefly within the first six months period.

Bacteriological Conversions: Bacteriological conversion occurred remarkably early in the course of treatment. Fifty-four per cent of cases were negative on smear and culture at six months of therapy. After six

*From the Piedmont Sanatorium.

TABLE 1—BACTERIOLOGICAL STATUS
Initially all sputa were positive on smear and culture

No. of Months Treatment	No. of Cases Studied	No. of Cases Positive	No. of Cases Negative	Per Cent Negative
0 — 3	46	25	21	45.6
4 — 6	35	16	19	54.2
7 — 9	29	17	12	41.3
10 — 12	18	13	5	27.7
13 —	6	4	2	33.3

months, however, a considerable number of patients became positive again and at the end of one year, only 27 per cent of cases had remained negative. No relapse occurred after a year (Table I).

Three patients who were sensitive to INH at the beginning of treatment converted and remained negative. Among five partially resistant cases, two converted within four months, but one became positive at eight months.

There was no significant difference in conversion rates between the two different doses of CS.

Cavity Closure: Thirty-one of the 46 cases had single or multiple cavities. Of these, only two achieved closure of cavities. One patient had maintained two cavities, 3 cm. in diameter each, throughout two years and six months of chemotherapy with SM, PAS and INH, closed these cavities within three months of CS-INH therapy. Eleven months later, however, they had reopened. Another patient with a cavity, 4 cm. in diameter, which had persisted for four years and four months of combined chemotherapy closed her cavity permanently after eleven months of CS-INH therapy. Both patients received 750 mgs. of CS daily and were resistant to INH. Two patients' cavities became smaller. Four patients' cavities became larger.

Roentgenographic Improvement: Both roentgenographic improvement and cavity closure were meager. Six patients, or 13 per cent, had moderate to marked improvement, graded as improvement greater than fifty per cent from the time of initial treatment and without spread of disease. Among these six patients, 3 received 750 mgs. of CS and 3 received 500 mgs. of CS. Majority of improvement occurred between three and six months. Five patients, or 10 per cent, had spread or deterioration.

Among three patients sensitive to INH, one improved markedly, two remained unchanged. Among five partially resistant, one improved moderately, two deteriorated and two were unchanged.

Toxicity: CS was discontinued in three cases: one because of convulsion and difficulty in talking after two weeks of treatment; one because of hyperreflexia and tremors after a week of treatment; and one because of emotional changes after two months of treatment. The former two cases received 750 mgs. of CS daily and the third case received 500 mgs. of CS. Three cases developed dizziness within two weeks of therapy. One patient had febrile reaction in a week. None of the entire group received pyridoxine.

Discussion

Bacteriological conversion was prompt and remarkable reaching its peak of 54 per cent at six months of therapy. Approximately 26 per cent of the cases became positive by the end of one year with no further relapse thereafter. It is suggested that the optimal duration of CS-INH therapy in resistant pulmonary tuberculosis should be six months followed by another regimen.

There were no significant differences between the two different doses of CS in the therapeutic efficacy and drug toxicity. The INH sensitive cases showed better results as might have been expected. Whether INH contributed to CS effects in the INH resistant cases, if any or how much, can not be determined without comparing the results of similar cases treated with CS alone.

SUMMARY

1. Forty-six Negro pulmonary tuberculosis patients, all of whom had received a long term chemotherapy and were treatment failures with combination of SM, PAS and INH, were treated with CS-INH.

2. Bacteriological conversion occurred in 54 per cent at six months of therapy, 27 per cent at twelve months with 26 per cent of relapse. No relapse was found after twelve months of therapy.

3. Moderate to marked x-ray improvement occurred in 13 per cent, relapse or deterioration occurred in 10 per cent. Cavity closure occurred in 3 per cent.

4. Treatment was discontinued in three cases, or 6 per cent, because of toxicity: one because of convulsion; one for hyperreflexia and tremors; and one due to emotional changes. Other toxic symptoms were mild, temporary, and negligible.

5. It is suggested that the optimal duration of treatment with CS-INH in resistant pulmonary tuberculosis should be six months.

6. There was no significant difference between the two different doses of CS, 750 mgs. and 500 mgs. daily, in therapeutic efficacy and drug toxicity.

RESUMEN

1. Se trataron con Cicloserina e isoniacida cuarenta y seis enfermos negros con tuberculosis pulmonar en los que el tratamiento a largo plazo con estreptomicina, PAS e isoniacida había fracasado.

2. A los seis meses de tratamiento se obtuvo la conversión bacteriológica en 54 por ciento, veintisiete por ciento a los doce meses con 26 por ciento de recaídas. No hubo recaídas después de los doce meses de tratamiento.

3 Mejoría radiológica moderada fué obtenida en 13 por ciento, recaída o empeoramiento en 10 por ciento. Cierre de cavidades en 3 por ciento.

4. Se suspendió el tratamiento en tres casos o sea el 6 por ciento, por toxicidad: una por convulsiones, una por hier-reflexia y temblores y una debido a cambios emocionales. Otros síntomas tóxicos son moderados, temporales y desdeñables.

5. Se sugiere que la duración óptima del tratamiento con Cicloserina e isoniacida en tuberculosis pulmonar con gérmenes resistentes sea de seis meses.

6. No hay diferencia de significación entre las dos dosis diferentes de 750 y 500 mg. por día en cuanto a eficacia y toxicidad.

RESUMÉ

1. 46 malades de race noire, atteints de tuberculose, qui avaient tous reçu une chimiothérapie longtemps prolongée, avaient été considérés comme des échecs thérapeutiques avec les associations streptomycine, P.A.S. et isoniazide, furent traités par l'isoniazide-cyclosérine.

2. La disparition des bacilles survint dans 54% des cas après six mois de traitement, 27% après douze mois avec 26% de rechutes. Aucune rechute ne fut enregistrée au-delà d'un traitement de douze mois.

3. Une amélioration de modérée à nette survint dans 13% des cas, une rechute ou une aggravation dans 10%. La fermeture de la cavité survint dans 3%.

4. Le traitement fut interrompu dans 3 cas, soit 6%; à cause de sa toxicité: dans un cas à la suite de convulsions, dans un autre à la suite d'hyperréflectivité et de tremblements, et dans un autre à la suite de manifestations psychiques. Les autres symptômes toxiques furent légers, temporaires et négligeables.

5. L'auteur suggère que la durée optimum du traitement par l'isoniazide-cyclosérine dans la tuberculose pulmonaire résistant aux autres médications devrait être de six mois.

6. Il n'y eut pas de différence nette selon les deux dosages différents utilisés de CS (750 mmg. et 500 mmg. par jour) ni dans l'efficacité thérapeutique, ni dans la toxicité.

ZUSAMMENFASSUNG

1. Es wurden 46 Neger mit aktiver Lungentuberkulose mit Cykloserin-INH behandelt, nachdem sie eine langzeitige Chemotherapie gehabt und auf die Kombination von Streptomyzin, PAS und INH nicht angesprochen hatten.

2. Bakteriologische Konversionen trafen bei 54% nach 6 Behandlungsmonaten, bei 27% nach 12 Monaten mit 26% Rückfällen auf. Es kam zu keinem Rückfall nach 12 Behandlungsmonaten.

3. Eine mässige bis ausgesprochene Besserung des Röntgenbefundes trat bei 13% auf, ein Rückfall oder eine Verschlechterung bei 10%. Cavernenverschluss trat bei 3% auf.

4. Die Behandlung wurde in 3 Fällen unterbrochen (6%) wegen toxischer Erscheinungen: einmal wegen Krämpfen, einmal wegen Reflexsteigerung und Zuckungen und einmal wegen emotioneller Veränderungen. Die anderen toxischen Symptome waren mild, temporär und unbedeutend.

5. Es wird angenommen, dass die optimale Behandlungsdauer mit Cykloserin in Verbindung mit INH bei Fällen mit resistenter Lungentuberkulose 6 Monate zu betragen hätte.

6. Hinsichtlich ihrer therapeutischen Wirksamkeit und Toxizität bestand kein wesentlicher Unterschied zwischen den beiden verschiedenen Dosierungen von Cykloserin-nämlich 750 mg und 500 mg täglich.

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Pulmonary Tuberculosis Treated with High Doses of INH plus Glutamic Acid

FRANCIS O. SEGARRA, M.D.* and DAVID S. SHERMAN, M.D., F.C.C.P.**
Mattapan, Massachusetts

Introduction

The generally accepted daily dosage of isonicotinic acid hydrazide for the treatment of pulmonary tuberculosis has been three to eight milligrams per milligram of body weight. Three essential factors justify this dosage: 1) there is the increased risk of toxicity in using higher doses of INH; 2) in vitro studies show that massive quantities of INH are not more effective than smaller quantities;[1] 3) many observers using various doses of INH failed to reveal any significant differences in the therapeutic results.

However, there is some indication that the optimal dose of INH has not been determined. First, high doses of INH in animal experimentations have been shown to be of benefit. Schmidt, working with monkeys, demonstrated clearly the advantages in using high doses of INH, 80 milligrams per kilogram of body weight, in comparison with the standard dose of 5 milligrams.[2] Secondly, the amount of INH administered and that found in the blood by the usual Kelly and Poet method parallel each other; however, this method detects the total amount of INH, including both the biologically active INH and the acetylated INH which has no biologic activity. The microbiologic assay or the chemical assay of Cuthbertson's picryl chloride method detects only the biologically active INH. It has been observed with microbiologic assay that the amounts of INH biologically active do not parallel the total amount of INH in blood, and consequently the amount of INH ingested. Furthermore, the biologically active amount is often extremely low. It is concluded from this fact that the present technique of administrating INH is rather blind and often insufficient. Finally, the toxicity of INH, the main obstacle to increasing the dose of the drug, must be reviewed.

Of the toxic symptoms of INH, the following are the most important: gastric intolerance, polyneuropathy, central nervous system intoxication, and liver damage.

The incidence of polyneuritis has been practically eliminated by the use of pyridoxine. The most serious reactions are those related to the liver and central nervous system. Cases of hepatitis with jaundice, due to INH, have been described, but they have been deemed exceptional.[3]

Central nervous system reactions such as convulsions and EEG abnormalities are more often seen, but still are infrequent.

Some of these symptoms are related to liver damage, i.e., the so-called cially in the cephalin-cholesterol flocculation tests, i. e., the so-called hepto-cerebral intoxication.[4] The EEG studies in this respect are of paramount interest. Foley, Watson and Adams in 1950 described for the first time a distinctive electroencephalographic pattern in comatose patients with severe liver disease.[5] At that time, these authors felt that

*Senior Staff Physician, Boston Sanatorium.
**Superintendent and Medical Director, Boston Sanatorium.

this encephalographic pattern was characteristic of hepatic coma; but in 1953, Adams and Foley reported that such changes could be seen in other conditions as well.[6]

Several other authors have observed the EEG changes described by Foley, Watson and Adams with elevation of the blood ammonia level in patients who were in hepatic coma. On the other hand, Poser[7] among others, observed the same EEG pattern in hepatic coma in patients having other diseases, but all of them had, in common, the presence of an elevated ammonia blood level higher than 135 gamma per 100 ml. The most accepted criterion is to consider the concentration of 200-400 mu. of ammonia per cent as a critical level beyond which the EEG tracings may rapidly deteriorate.

The role of ammonia in the symptoms of hepatic coma will not be discussed here; however, the ideas of Walsh[8] in regard to the therapeutic effect of sodium glutamate in hepatic coma must be commented upon. According to this English author, sodium glutamate can possibly work in two ways: first, it could combine with ammonia to form glutamine, which transports ammonia to the kidney for excretion; second, by the action of sodium glutamate on the Krebs Cycle, (due to the fact that blood-pyruvate is considerably raised in hepatic injury). In this case, sodium glutamate by transamination with pyruvic acid could form alpha-ketoglutaric acid, an intermediate of the Krebs Cycle, and in this way remove ammonia.

Furthermore, it has been mentioned repeatedly that in rabbits glutamic acid, if administered in adequate amounts, is capable of preventing convulsions caused by ammonium chloride.

Toxicity in the central nervous system due to INH therapy is probably produced by ammonia arising from the degradation process of INH metabolism. This latter was suggested by Trabuch.[9]

On the basis of these facts and hypotheses, Cedrangolo[10] undertook (in 1952) a series of studies in which he gave isonicotinic acid hydrazide and glutamic acid together, in order to lessen the degree of toxicity.

The results of the animal experimentation[11,12,13] and the clinical trials[14,15] have been striking and of the greatest interest. As a result of these studies, we made a clinical trial of the Cedrangolo method in our institution. Our purposes were to study the toxicity of INH in humans, and in particular, upon the liver and central nervous system, to take advantage of the supposed protective action of glutamic acid, and to investigate the action of the high dosage of INH upon the clinical and radiological picture of pulmonary tuberculosis.

Materials and Methods

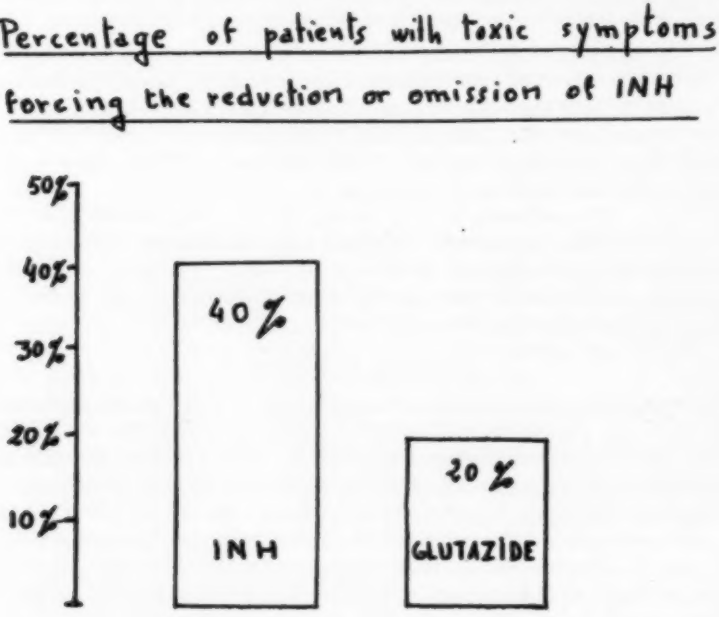
Fourteen male patients were chosen to carry out this study. Ages ranged from 23 to 69 years, with an average of 50 years. Most of them were readmissions to the sanatorium; that is, with old and far advanced pulmonary tuberculosis. All of them had been treated previously with 600 mgs. of INH daily for at least six months. They had also been given other accompanying therapy such as streptomycin, paraminosalicylic acid, and pyridoxine. No marked effect upon either the clinical or radiological pictures were expected. Attention was focused usually on the toxi-

city of the INH, as said before, on the central nervous system and the liver. Monosodium glutamate was used for the stated protection against the toxicity. Nine patients received 20 mgs. of INH per kilogram of body weight daily, together with the previous accompanying medications, streptomycin or PAS, but without glutamic acid. They served as a control group. The other five received 20 mgs. of INH per kilogram of body weight daily, plus monosodium glutamate 10 mgs. for each milligram of INH.

Glutazide™ was used. Each capsule contains 50 mgs. of INH plus 500 mgs. of monosodium glutamate.

Five additional patients from the control group were later added to the treatment group taking the glutazide. Of these, three were added to the treatment group because intolerance developed to the INH alone; the other two were added to the treatment group purposely to see whether a difference could be noted resulting from the type of medication administered in the same patient. The total number receiving glutazide, therefore, was 10.

Pyridoxine 100 mgs. daily was given to all patients. The duration of treatment varied between 3 and 10 months, except for case No. 5, to whom medication was omitted definitely the day after it was started. Several laboratory studies were carried out with special attention to those concerning liver functions; as for example, total protein, AG ratio, alkaline phosphatase, fasting blood sugar, BSP test, cephalin-cholesterol flocculation tests, thymol torbidity, ammonia blood level, white blood count, hemoglobin, and hematocrit. For the determination of blood ammonia levels, a modification of the Conway microdiffusion method has been used by which ammonia levels above 125 gamma



could be detected. All but one of the patients taking glutazide were closely followed by electroencephalographic tracings. Those taking INH alone, also had EEGs but only occasionally. Bacteriological studies for acid fast bacilli were carried out periodically at monthly intervals.

Results

1. Toxic Effects

Nine patients were treated without glutamic acid, and served as a control group. In four of them, cases No. 1, 4, 5, and 9, INH had to be omitted or reduced due to side effects.

CASE 1: complained of slight tinnitus, headaches, slight amnesia, sleepiness and drowsiness one month after starting high doses of INH (1100 mgs. daily). These symptoms, however, were mild, and medication was kept on for two months more. At that time, a "spell" of weakness and drowsiness without loss of consciousness or convulsions occurred; neurological examination was negative. The medication was stopped and the symptoms were gone the next day. Later on, medication was resumed, this time accompanied with glutamic acid (Glutazide). The dose of INH this time was 600 mg., and then it was increased 50 mg. every three days until the full dose of 20 mgs. per kg. of body weight was reached. Thirty-five days later, a few after the full dose of INH had been reached, he complained again of sleepiness and drowsiness. Glutazide was omitted; the patient felt all right the next day. Unfortunately, no EEG studies could be performed. It must be pointed out that he had a history of convulsive seizures before developing clinical tuberculosis; and once, about nine months previous, had a convulsion when taking 600 mgs. of INH.

CASE 4: The day after a high dose of INIH (1180 mgs.) was given to case 4, itching, headache, and feeling of pins and needles around the eyes developed. INH was omitted, and the symptoms vanished quickly. At a later date, INH with glutazide were started, and in increasingly progressive doses; namely, 600 mg. of INH daily for three days, then augmenting 50 mg. INH every three days until the dose of 20 mgs. per kg. of body weight was reached. At this time, no untoward effect was observed. Glutazide was administered for six months.

CASE 5: presented the severest complications, convulsions and loss of consciousness for a few minutes the night of the very day that high doses of INH were started (1800 mgs. daily). INH was omitted at once, and headaches persisted for a few days. It must be stressed again that he had a history of convulsions months before (the real nature of which was unknown).

CASE 9: was started on INH (1800 mgs. daily) and on the first day this was accompanied by sleepiness and drowsiness and dizziness. On the third day of the medication, he had a loss of consciousness for a few seconds. The medication was omitted, and he improved immediately. The EEG tracings before the increase of INH were normal; those taken 24 hours after receiving the medication showed a definite abnormality consisting of slow wave activity changes similar to those seen in hepatic coma. An EEG taken five days after omission of INH was almost normal; that taken 19 days later was completely normal. INH was resumed afterwards together with glutamic acid (Glutazide), starting with 900 mgs. of INH daily, and increasing the dose progressively until 1800 mgs. of INH daily was reached. No clinical symptoms were evidenced, except for persistent nightmares. However, the toxicity upon the central nervous system could be detected through the EEG tracings. All the EEG's taken during the treatment were abnormal, suggesting metabolic encephalopathy. No neurological sign was observed, he felt perfectly well during the period on medication. Laboratory tests were all reported as normal. Glutazide was continued for four months; then INH was reduced to 600 mgs. because the EEG changes became more marked. An EEG taken a few days after reduction of medication showed an absolutely normal tracing.

Patients 7 and 8 in the control group were shifted purposely to glutazide one month after being started on INH. They did not present any side effects, and all EEG's were read as normal.

The three remaining patients of the control group were kept on INH all the time without glutamic acid. None of them presented significant complaints; the occasional EEG did not show any abnormality.

Ten patients received Glutazide, half of them having been mentioned above in the control group (cases 1, 4, 7, 8, and 9). Of the five started directly on high doses of Glutazide, cases 10 and 12 manifested side effects. Case 10 was complaining of severe insomnia while taking ordinary doses of INH; on the other hand, he could sleep well soon after high doses of Glutazide were begun. Otherwise, he felt normal. The EEG studies revealed an abnormal tracing three days after Glutazide was commenced. Changes consisted of a possible presence of metabolic encephalopathy. Medication, however, was maintained for four months. All the subsequent EEG's were interpreted as normal; and all laboratory tests were reported as normal. Case 12 pre-

sented slight sleepiness during the first three weeks of Glutazide treatment. The symptoms disappeared later on; all EEG studies and laboratory tests were normal.

In summary, four out of nine (40 per cent) of the patients treated with INH at a dose of 20 mg. per kilogram of body weight daily, and without monosodium glutamate, developed toxic symptoms severe enough to stop or reduce medication. On the contrary, in two of the 10 (20 per cent) treated with Glutazide, medication had to be reduced because of the toxic effects (cases 1 and 9). Two other patients had minimal side effects which did not interfere with the high doses of medication.

Finally, it has been remarkable that case 4 had no untoward reaction while being treated with Glutazide, and that case 9, although presenting abnormal EEG tracings, did not complain of toxic symptoms while on Glutazide. These two patients, as it has been mentioned before, presented toxic symptoms while receiving INH alone.

All the toxic symptoms and untoward effects encountered relate to the central nervous system. The peculiar feature of the side effects is that they appeared promptly after medication was started. In only case 1 did they appear as much as a month later. They vanished once the medication was omitted.

Clinical Results

None of the patients studied presented clinical symptoms with the exception of cases 10 and 11, who complained of moderate productive cough. Definite relief was obtained on glutazide treatment. No conclusion can be made from this brief observation. Most of the patients on Glutazide had markedly increased appetites soon after starting the medication. Two taking INH only had increase of appetite also, but to a lesser degree. Increase in weight also has been remarkable in those taking Glutazide, over and above those treated with INH alone. Euphoria was noticeably improved in patients on Glutazide.

Laboratory Tests

All of the laboratory tests remained within normal limits except for cephalin-cholesterol flocculation tests. In seven of the 14 patients, cephalin tests were positive before starting the trial (with values between 1 and 3 plus). Once medication was started, a slight tendency toward positivity could be observed in this test. Ten out of the 14 presented positive values; one of them (case 11), without any clinical or EEG signs, increased from 3 plus before Glutazide to 4 plus afterward.

There was no relation between toxic symptoms and the results of cephalin flocculation tests. It must be mentioned that 50 percent of our patients were chronic alcoholics, and possibly to begin with, the liver should not be considered entirely normal. Bacteriological studies for tuberculosis bacilli were done. Seven out of the 14 patients were positive for acid fast bacilli before starting the trial. Three of them were still sensitive to INH therapy, and the other four were resistant. None of them turned negative in the course of the high dose of INH therapy.

Radiological Results

Serial chest films of these patients showed that no particular change could be considered relating to treatment. None could be considered as showing any real improvement, except for case 9, in whom a cavity in the left upper lobe was noted to be reduced one-third in size in the four months the patient received Glutazide.

Discussion

In four out of nine cases (40 per cent) treated with 20 milligrams of INH per kilogram of body weight, the medication had to be omitted or reduced because of untoward side effects. On the contrary, of 10 patients taking INH plus glutamic acid

(Glutazide), in only two (20 per cent) cases was medication reduced (Figure 1). One case of convulsions and one of loss of consciousness were encountered among patients taking INH alone. None of these accidents was seen in the group on Glutazide. One case in the control group, who complained of headaches, parathesias around the eyes, and itching while treated with INH alone, was symptom free when treated with Glutazide. However, Glutazide was given to this patient in increasing doses slowly. Another patient, belonging to the control group, complained of sleepiness, drowsiness, dizziness, and finally loss of consciousness. He did not complain of symptoms while taking Glutazide, although his EEG tracings were abnormal and medication had to be reduced eventually. In this case, too, Glutazide was given in slowly increasing dosage. Only one who complained of headache, slight tinnitus, slight amnesia, sleepiness and drowsiness while on INH alone, had the same symptoms when treated with Glutazide, even though the latter was given in slowly increasing doses. EEG abnormalities were definitely seen in only one case among 14; in this case, the same abnormalities were present with or without glutamic acid, and consisted of slow activity changes similar to those seen in hepatic coma. Another case of the group on glutazide showed some abnormalities of the EEG tracings, but this was on only one occasion. In spite of continuing the medication, the EEG tracings were repeatedly normal.

Cephalin-cholesterol flocculation tests had a tendency to become positive, but no definite impairment of liver function could be found. Ammonia levels were consistently normal by means of the Ammon-test. They were, therefore, under 130 micrograms per milliliter. No gastrointestinal symptoms or polyneuropathy were observed.

The untoward effects appeared the first day medication was increased. In only one case did they become apparent as long as one month following treatment. Another peculiarity of the untoward effects observed was that they disappeared, without further consequence, immediately after INH was omitted.

There was remarkable improvement in appetite, weight, and feeling of well being, with a clear advantage for the patient taking Glutazide in comparison with those on INH alone. At present, we cannot explain this. Psychologic influences cannot be ruled out, but the facts were evident.

The radiological results were practically nil, as it was anticipated when dealing with patients with chronic far advanced pulmonary tuberculosis, who have been treated previously, most of them having been on three drugs for long periods of time.

Concerning the sputum studies, nothing can be concluded because only seven cases were positive to begin with, and only three of these were sensitive to INH; the others were resistant. Nevertheless, no case turned negative during the course of the medication.

Conclusions

a) Th toxicity due to isoniazid is lessened by the simultaneous administration of glutamic acid at a rate of 10 mg. for each 1 mg. of INH.

b) Patients on a high dosage of INH plus glutamic acid (Glutazide) present a remarkable improvement of appetite, weight, and feeling of well-being. This is definitely more noticeable than those taking INH without glutamic acid.

c) INH at a dose of 20 milligrams per kilogram has to be given at a slowly increasing level of dosage even when administered together with glutamic acid.

d) The toxicity of INH in this series of 14 patients has been practically limited to the central nervous system. The blood ammonia levels have been constantly within normal limits. Therefore, the supposedly toxic action of the ammonia anticipated from the Italian literature by the degradation of the molecule of INH seems unlikely to us. We believe rather in a direct action of the INH on the central nervous system.

e) The mechanism of action of the glutamic acid in lessening the toxicity of the INH is unknown in our opinion. Considering that the toxic symptoms of the INH are not due to the increasing level of ammonia in the blood, the idea of the diaminazation by the glutamic acid to form glutamine is no longer tenable in this case.

f) INH at doses of 20 milligrams per kilogram does not represent any advantage comparatively to the standard doses in treatment of patients with older disease medicated previously for a long time.

g) It is still of great interest to find out the true therapeutic value of INH in high doses of 20 milligrams per kilogram or even higher. For that, cases with new, or fresh, disease should be tried. Giving the medication in slowly increasing doses, together with glutamic acid, at a rate of 10 milligrams for 1 milligram of INH, and with pyridoxine, the danger of serious toxic effects due to INH are practically nil.

SUMMARY

A study of the toxicity of INH given at high dosage and simultaneously administered with glutamic acid has been carried out.

Fourteen patients with chronic far advanced pulmonary tuberculosis, previously treated with antibiotics at standard doses, were treated with INH at daily doses of 20 milligrams per kilogram of body weight. Nine of them received INH without glutamic acid and served as a control group. Five others, plus five others later added

from the control group, were treated with INH at 20 milligrams per kilogram together with glutamic acid, at a rate of 10 milligrams per each milligram of INH.

All the patients received 100 milligrams of pyridoxine daily. Liver function tests as well as serial EEG tracings were performed. Glutamic acid lessens notably the toxicity due to INH.

It is of great interest that use of glutamic acid remarkably improved patient appetite, weight gain, and feeling of well-being.

ACKNOWLEDGMENT: EEG studies have been done by Dr. Donald H. Osterberg, Neurological Unit, Boston City Hospital.
We are indebted to the Gray Pharmaceutical Co., Inc., for its kindness in supplying us with Glutazide medication.

RESUMEN

Se ha llevado a cabo un estudio de la toxicidad del INH a alta dosis administrado simultáneamente con ácido glutámico.

Se trataron 14 enfermos de tuberculosis pulmonar muy avanzada crónica antes tratados con antibióticos a las dosis corrientes, usando después nosotros INH a las dosis diarias de 20 miligramos por kilo de peso.

Nueve de ellos recibieron INH sin ácido glutámico y sirvieron como control. Otros cinco, más cinco adicionales, tomados más tarde del grupo de control, se trataron con INH a 20 mg. por kilo agregando ácido glutámico a la dosis de 10 miligramos por cada miligramo de INH.

Todos los enfermos recibieron 100 miligramos de piridoxina diarios. Se hicieron pruebas de función hepática así como EEG en serie. El ácido glutámico disminuye notablemente la toxicidad debida a la INH.

Es de gran interés hacer notar que el ácido glutámico mejoró notablemente el apetito, el aumento de peso y la sensación de bienestar.

RESUMÉ

L'auteur a mené une étude sur la toxicité de l'isoniazide utilisé à hautes doses et administré en association avec de l'acide glutamique.

14 malades atteints de tuberculose pulmonaire chronique très avancée, ayant reçu antérieurement des antibiotiques aux doses standard, furent traités par l'isoniazide aux doses quotidiennes de 20 mmg. par kilogramme de poids corporel. Neuf d'entre eux reçurent de l'isoniazide sans acide glutamique et servirent de témoins. Cinq autres, ainsi que cinq malades ajoutés plus tard et pris parmi les témoins, furent traités par l'isoniazide à la dose de 20 mmg. par kilogramme associé à l'acide glutamique, au taux de 10 mmg. par milligramme d'isoniazide.

Tous les malades reçurent 100 mmg. de pyrydoxine chaque jour. On pratiqua les tests de la fonction hépatique, ainsi que des tracés électrocardiographiques en série. L'acide glutamique diminue notablement la toxicité de l'isoniazide.

Il est d'un grand intérât que l'emploi de l'acide glutamique améliore l'appétit des malades, le gain de poids, et la sensation de bien-être.

ZUSAMMENFASSUNG

Es wurde eine Untersuchung der Toxizität von in hohen Dosen gegebenen INH unter gleichzeitiger Verwendung von Glutaminsäure vorgenommen.

14 Patienten mit chronischer, weitfortgeschrittener Lungentuberkulose, die bis dahin mit Antibiotica in Standartdosen behandelt worden waren, erhielten INH in täglichen Dosen von 20 mmg pro Kilogramm Körpergewicht. Neun von ihnen erhielten INH ohne Glutaminsäure und dienten als Vergleichsgruppe.

5 weitere, sowie noch 5 später aus der Vergleichsgruppe hinzugenommene Kranke, erhielten INH 20 mmg pro Kilogramm zusammen mit Glutaminsäure in einer Höhe von 10 mmg pro Milligramm INH.

Alle diese Kranken erhielten 100 mmg Pyrdoxin täglich. Es wurden Leberfunktionsproben ebenso wie serienmässige EEG laufend ausgeführt. Glutaminsäure setzt die durch INH bedingte Toxizität beträchtlich herab.

Es ist sehr bemerkenswert, dass die Verwendung von Glutaminsäure Appetit, Gewichtsanstieg und Wohlbefinden der Patienten beträchtlich steigert.

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Some Aspects of Chronic Respiratory Diseases in Coalminers in New South Wales, Australia

K. G. OUTHRED, M.B. B.S., F.C.C.P., and M. J. FLYNN, M.B. B.S.
Sydney, Australia

SYNOPSIS

Pneumoconiosis of coalminers appears to be a conglomerate of fibrosis, emphysema, bronchial obstruction and simple clogging of the lung tissues and air spaces with dust. The prevalence of pneumoconiosis and of chronic obstructive bronchitis and emphysema amongst New South Wales coalminers is considered. Schemes for diagnosis and assessment of severity are presented, along with some results of therapy and of post mortem studies. Field tests of lung function are evaluated in comparison with more complex laboratory investigations.

Coal dust has long been classified amongst the so-called "inert" dusts, but it is now recognized, largely as a result of the work of industrial pathologists — Cummins and Sladden (1930), Badham and Taylor (1933 and 1936), Hart and Aslett (1942), Gough (1947 and 1949) and Heppleston (1953 and 1954) — that its inhalation in sufficient quantities over sufficiently long periods produces a pneumoconiosis which in its typical form is quite distinct from silicosis.

Pathologically it is characterized by a stellate type of nodule without redundant collagenous fibrosis or hyalinisation, and by an earlier development of associated pulmonary emphysema (usually initially of focal type and closely surrounding the stellate nodules) than is the case in silicosis. Radiologically in its typical form the nodular opacities are softer than in classical silicosis and of very small (pinhead) size, occurring singly or as rosette-like aggregates; and massive shadows, if present, tend to be softer, more sharply outlined, and more homogeneous, and to be separated from the chest wall by a clear, often emphysematous zone.

Clinically it differs from silicosis in two principal ways; complicating tuberculosis is rare, and there is a greater tendency, especially in men over 45, to produce respiratory invalidity with only slight reduction of the life span.

The question of the relationship of tuberculous infection to the pneumoconiosis of coalminers has been studied intensively in the United Kingdom and elsewhere. There is a strong probability that the areas of progressive massive fibrosis in coalminers' lungs represent accumulations of dust in and around the scars of old infection, usually tuberculous. Evans (1951) has isolated from various coals a substance, which he calls "vitricin," which appears to possess antibiotic properties against the tubercle bacillus; this offers a possible explanation of the observed tendency in coal dusted lungs to arrest of infection (the opposite of what occurs in silicosis).

Where invalidity is present in coalminers, it is in most cases due to resistance to breathing. In these cases pulmonary emphysema, chronic bronchial obstruction, or recurrent pleurisy or other non-tuberculous respiratory infection is usually manifest in addition to the radiological fibrosis.

We consider the penumoconiosis of coalminers to be a composite in varying proportions of fibrosis, emphysema, bronchial obstruction, and simple clogging of the lungs with dust, each of which may cause resistance to breathing and impairment of lung function.

In the coalfields of New South Wales, the prevalence of chronic bronchitis and pulmonary emphysema (without radiological pneumoconiosis) is highest where the incidence of pneumoconiosis is greatest. Our miners have not been exposed to atmospheric pollution above ground. Whilst infections, climatic conditions, and cigarette smoking play a role, coal dust has probably been an aggravating factor in many instances.

Pemberton (1956), Higgins (1956) and Carstens (1957) under certain circumstances regard bronchitis and emphysema in miners as occupational diseases.

The Prevalence Of Chronic Respiratory Diseases In New South Wales Coalminers

The coalmining industry employs 17,000 men, 12,000 of whom work underground, producing about 17,000,000 tons of black coal annually.

Compensation has been awarded to 1070 miners and ex-miners with pneumoconiosis and/or emphysema over the period 1934-1957. More than half the cases of compensation for industrial chest disease are derived from the southern coalfields (Wollongong area), which employ only one quarter of the total work force. In this area high atmospheric dust and CO_2 concentrations were common in earlier years.

The present extent of pneumoconiosis amongst miners still at work in New South Wales is approximately 3.0 per cent of all employees, of whom 1.25 per cent are radiological Category Two or worse, and about two per thousand have Progressive Massive Fibrosis.

There has been a considerable reduction in prevalence of pneumoconiosis in New South Wales coalminers in comparison with figures produced by George and Wallman in 1948. This is the result of a 10 year programme of dust control, coupled with restrictions placed on the entry of partly dusted men into the industry and the removal of dusted men through retirement or compensation.

The incidence of tuberculosis in active or arrested form is slightly lower than that of the general community (as found from mass surveys) (Table 1).

TABLE 1 — PREVALENCE OF TUBERCULOSIS AMONGST 3125 SOUTHERN COALFIELD EMPLOYEES EXAMINED BETWEEN 1949 AND 1951

	Prevalence	Community Rate (Mass Surveys)
Active Tb.	0.42 per cent	0.5 per cent
Inactive Tb.	1.3 per cent	1.5 per cent

In the sample survey of 1,500 miners by George and Wallman in 1948 the prevalence of bronchitis was found to be about 10 per cent. The results of recent periodic medical examinations show that the prevalence, exclusive of those without physical signs, is 7 per cent, with severe disability in 1.5 per cent. The general community rate for the district is not accurately known but it is believed to be at or about this latter level.

Diagnosis And Classification Of Patients

In the chronic respiratory diseases of miners, systems of grading of radiological extent of disease have been used for several decades with varying success. In 1950, the International Labour Office Sydney classification was adopted in the New South Wales coalmining industry.

We have endeavoured to carry the principle of grading of chronic respiratory disease in coalminers into the clinical field. We believe it is possible to evaluate separately the emphysema and bronchitis components and have evolved useful working classifications based on four grades of severity in each case.

Likewise we have, using in the field simple respirometer tests only, classified the results into four grades of impairment of respiratory function, in somewhat similar fashion to Motley (1953). According to percentage loss of function, patients have been classified into four grades of respiratory impairment as shown in Table 2.

TABLE 2 — BASIS OF GRADING FOR SPIROMETRIC MEASUREMENTS AS PERCENTAGE OF PREDICTED VALUE FOR AGE AND BUILD

Respiratory Impairment		Grade 0 (R0)	1 (R1)	2 (R2)	3 (R3)	4 (R4)
M.B.C.	(Motley's Formula)	> 75% PV*	75 - 55	55 - 40	40 - 30	<30%
V.C.	(Baldwin's Formula)	>100% PV	100 - 80	80 - 70	70 - 60	<60%
T.V.C.	(1 sec) (Gaensler)	> 70% actual	70 - 60	60 - 50	50 - 40	<40%

*PV=Predicted value for age and body build.

The classifications we use are therefore as follows:

Pneumoconiosis:	I.L.O. Categories 1, 2, 3, A, B, C, D.	(e.g. P2)
Emphysema:	Grades 1, 2, 3 and 4.	(e.g. E3)
Bronchitis:	Grades 1, 2, 3 and 4.	(e.g. B2)
Respiratory Function:	Grades 1, 2, 3 and 4.	(e.g. R3)

To quote examples, a patient classified as P2 B2 E2 R2 has a simple pneumoconiosis with moderate bronchitis and emphysema, and moderate ventilatory impairment judged by simple tests to be described. A patient E4 R4 would have cor pulmonale and grossly defective respiratory function.

A grading of 0 in any of the above groups implies absence of the particular abnormality.

Recognition Of Emphysema And Bronchitis — Criteria For Grading

There is often difficulty in recognizing slight and moderate degrees of emphysema, and Table 3(a) represents the basis of our grading of emphysema.

Table 3(b) represents the basis of our grading of bronchitis.

Respiratory Function — Field Studies

In the New South Wales coalmining industry respirometer tests have been introduced into the field work of the Joint Coal Board medical service, and have become accepted as of equal standing to the chest x-ray film as an ancillary supplement to the clinical examination. Selected workers have been referred for more intensive studies (blood gases, lung volumes, helium or nitrogen mixing curves, diffusion and the work of breathing) to research laboratories in Sydney.

TABLE 3 (a) — EMPHYSEMA
Basis of Diagnosis and Grading of Severity

SYMPTOMS	Grade 1.	2.	3.	4.
1. Dyspnoea	+	++	+++	++++
2. Tight feeling in chest	+	+	++	++
3. Cough and expectoration	+	+	+	+
4. Nocturnal choking turns	+	+	+	+
5. Chest wall pain	+	+	+	+
6. Dizziness (with cough), syncopal turns	−	+	+	+
PHYSICAL SIGNS				
The four signs most uniformly present at all stages are: Hyperresonance of lungs; Loss of cardiac and liver dulness; Soft breath sounds; Soft heart sounds				
General Inspection.				
1. Observed breathlessness, inspiratory and expiratory prolongation, see-saw rhythm	−	+	++	++
2. Increased resting respiration rate (normal up to 18/minute)	−	+	+	++
3. Undue tachypnoea and dyspnoea on exercise	+	+	++	+++
4. Laryngoptosis	−	+	++	++
Inspection of Chest.				
1. Inspiratory position of thorax	−	+	++	++
2. Absent cardiac impulse at normal apical area	−	±	+	+
3. Increased pulsation in upper epigastrum	−	±	+	+
Abnormalities of Thoracic Movement.				
1. Rigidity of thorax, movement "en bloc"	−	+	++	++
2. Use of accessory muscles of respiration	−	±	+	++
Palpation.				
1. Diminished chest expansion (measured)	+	++	+++	++++
2. Diminished vocal fremitus	−	+	++	++
3. Absent cardiac apical impulse	−	−	+	+
Percussion of Chest.				
Hyperresonance, extended areas of resonance	+	++	+++	++++
Auscultation.				
1. Soft breath sounds	+	++	+++	++++
2. Soft heart sounds (a) apex, (b) base	±(b)	−(a) +(b)	+(a) +(b)	++(a) ++(b)
3. Diminished vocal resonance	−	+	++	++
Other Signs.				
1. Cyanosis	−	−	+	++
2. Clubbing of fingers, toes	−	−	−	+
3. Wasting	−	+	++	+++
4. Fluctuation of Blood Pressure (varies with respiration)	−	−	+	+
5. Ocular fundi — dark, with swollen veins	−	−	+	+
6. Polycythemia	−	−	−	+
7. Signs of congestive C.F. (earliest sign increased Jugular V.P.)	−	−	−	+
ELECTROCARDIOGRAPHIC SIGNS				
1. Vertical position of heart	+	+	+	+
2. Clockwise rotation (viewed from below)	−	+	+	+
3. P. Pulmonale — 2 mm.+ (leads II and aVF)	−	−	+	+
4. Fading amplitude of R. Waves V4 — V6	−	+	+	+
5. Persistent S. Waves V5 — V6	−	−	+	+
6. R — S ratio in Lead VI, tends to equal V6	−	−	+	+
7. R.B.B. pattern in VI, V2, V3R, or 3V3	−	−	+	+
8. Inversion of T Waves in VI, V2 and perhaps V3 with acute infection	±	+	+	+
with no infection	−	−	−	+

RADIOLOGICAL SIGNS				
P.A. Film.				
1. Low, flat diaphragm (relative to build)	+	++	+++	++++
2. Vertical central small heart shadow	−	+	+	+
3. Increased contrast between lung fields and bony structures; absence of vascular markings	+	++	+++	++++
4. Enlargement of lung fields in comparison with mediastinum, roomy thorax, wide rib spaces	+	+	+	+
Lateral Film.				
1. Increased anteroposterior diameter	+	+	+	+
2. Increased area and translucency of antero and retro-cardiac spaces		+	+	+
Fluoroscopy.				
1. Increased transillumination of lung fields	+	++	+++	++++
2. Diminished excursion of diaphragm; paradoxical movements		+	++	+++
3. Pulmonary conus enlarged and pulsating			+	++
4. Enlargement of right ventricle			+	+

TABLE 3 (b) — BRONCHITIS
Basis of Diagnosis and Grading of Severity

SYMPTOMS	Grade 1.	2.	3.	4.
1. History of Bronchitis	+	+	+	+
2. Cough and Wheeze, with disturbance of sleep	+	++	+++	++++
3. Tightness in chest and anterior chest soreness		+	+	+
4. Expectoration of sputum which is at least occasionally mucopurulent	+	+	+	+
SIGNS				
1. Reduced chest expansion			+	+
2. Audible wheeze, or stridor			+	+
3. Accessory respiration			+	+
4. Bronchial breath sounds	+	+	+	+
5. Inspiratory and expiratory rhonchi or basal moist rales		+	+	+
E.C.G. As for right heart strain and cor pulmonale. Abnormal signs present only in advanced stages or with superadded acute respiratory infections.				
X-ray Abnormalities — Nil.				
Fluoroscopy — paradoxical diaphragmatic movements.			+	+

In the assessment of respiratory function in pneumoconiosis and emphysema it is felt that considerable reliance can be placed on the Maximum Breathing Capacity (M.B.C.) supported by the Timed Vital Capacity (T.V.C.) (Gaensler, Kennedy 1952) and Vital Capacity (V.C.) We considered, like Donald (1953), that the M.B.C. was the best single test available for general clinical use, but recently have been impressed with the greater sensitivity and acceptibility of Fowler's mid-expiratory flow-tests (1955).

The prediction formula used by Baldwin and Cournand (1948) for M.B.C. and V.C. yield figures much lower than we find in our normal patients. The prediction formula for M.B.C. which Motley (1953) obtained from his investigation of coalminers is applicable to our patients.

Tables 4 and 5 show an analysis of the results of these simple function tests as carried out routinely on 1000 normal males. These figures have been confirmed by additional tests performed by our staff on 300 normals and 300 patients with respiratory disorder.

The effect of pneumoconiosis and bronchitis and emphysema on maximum breathing capacity in our coalminer patients is shown in Tables

6 and 7. Patients with pneumoconiosis may have normal M.B.C. but if, in addition, there is bronchitis or emphysema, the M.B.C. is always considerably lowered.

TABLE 4 — ANALYSIS OF MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY OF 1020 NORMAL MALES

Age Group	No.	M.B.C. Litres/min. Actual Mean	S.D.	Per Cent Predicted Mean	S.D.	Vital Capacity Litres Actual Mean	S.D.	Per Cent Predicted Mean	S.D.
15-19	149	138	16	92	12	4.92	0.76	112	16
20-24	235	142	23	94	14	4.98	0.69	116	15
25-29	206	144	21	96	15	4.98	0.64	117	14
30-34	146	140	22	95	15	4.84	0.52	116	14
35-39	102	135	21	95	17	4.61	0.68	114	16
40-44	74	132	21	96	15	4.62	0.64	118	14
45-49	46	121	19	93	17	4.54	0.49	116	17
50-54	44	119	21	94	19	4.31	0.60	112	13
55-59	18	112	22	93	19	4.18	0.58	108	15

Method: Patient Standing Apparatus: Collins 13.5 Litre Spirometer

Prediction Formula: Motley MBC = (97 — Age × 0.5) × B.S.A. m^2

Baldwin & Cournand VC = (27.63 — Age × 0.112) × Height cms.

TABLE 5 — ANALYSIS OF THE 1-SECOND TIMED VITAL CAPACITY OF 506 NORMAL MALES

Age Group	Number Normal Miners	1-Second T.V.C. as mean % of Actual V.C.	Standard Deviation
15-19	86	94	6
20-24	124	91	7
25-29	114	88	6
30-34	72	87	6
35-39	40	85	6
40-44	35	82	7
45-49	17	83	7
50-54	16	79	6
55-59	8	77	8

Method: Patient Standing Apparatus: Gaensler Vitalometer

TABLE 6 — EFFECT OF PNEUMOCONIOSIS ON LUNG FUNCTION (170 WORKING MINERS)

Pneumoconiosis Category	M.B.C. Per Cent PREDICTED (Motley) 100+	100 — 81	80 — 61	60 — 41
0 — 1	10	12	11	12
1	15	26	28	15
2	1	10	17	13

TABLE 7 — EFFECT OF BRONCHITIS AND EMPHYSEMA IN ADDITION TO PNEUMOCONIOSIS ON WORKING MINERS' MAXIMUM BREATHING CAPACITY. (174 WORKING MINERS)

Classification	M.B.C. Per Cent PREDICTED 100+	100 — 81	80 — 61	60 — 41
P1 B0 E0	25	38	35	27
P1 B2 E2	—	—	4	6
P2 B0 E0	1	10	11	5
P2 B2 E2	—	—	4	8

Special Respiratory Function Tests

As stated earlier, because of the limitations of the respirometer, we have referred selected patients presenting various grades of respiratory disability to research units in Sydney for more intensive study.

Ninety-nine patients (males) were investigated, 72 at the Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, and 27 at the University of Sydney Medical School. There were four normal patients as controls and 95 classified as having pneumoconiosis, bronchitis and/or emphysema, and the overall picture was a mixture of these conditions. Cardiovascular diseases were excluded as far as is possible in dealing with such age groups.

In the evaluation of the laboratory studies carried out in Sydney, the following standards of normality were used:

Lung Volume	RV/TLC	40 per cent or less
Alv. Ventilation	DS/VT	35 per cent or less
Venous Shunt	QVA/QT	7 per cent or less
Diffusion	D.CO	10 or more
and	$D.O_2$	12 or more
Gas Exchange	Art. O_2 Saturation	94 per cent or more
	Art. CO_2 Tension	43 mms or less

Compliance of Lungs 0.12 – 0.33 Litres/cm H_2O

Work of Breathing (Rest) 0.2 – 0.5 KgM/Min.

These standards are considered to be liberal and to allow a satisfactory margin for technical variation.

Space does not permit the publication of clinical histories or details of all tests carried out. This information is available on request.

Table 8 correlates the results of individual tests performed in the Sydney Clinics with the overall classification previously given in the Southern District studies of the cases. The number of cases in which the findings were normal (N) and abnormal (A) are shown for each test.

TABLE 8 — CORRELATION OF SPECIAL LUNG FUNCTION TESTS WITH FIELD TEST GRADING OF RESPIRATORY IMPAIRMENT

N = Normal Result A = Abnormal Result

Lung Function Laboratory Test	Field Tests—Grade of Respiratory Impairment									
	0		1		2		3		4	
RV/TLC	N5		N9	A3	N2	A5	A2			A1
DS/VT	N6	A5	N13	A19	N5	A21	N1	A8		A4
QVA/QT	N5	A1	N13	A8	N4	A15		A12		A5
O_2 Saturation	N13		N20	A9	N13	A16		A14		A5
CO_2 Tension	N6	A2	N19	A3	N4	A6	N6	A7	N1	A13
$D.O_2$		A3	N18	A2		A8	N3	A9		A4
D.CO	N8	A2	N16	A8	N10	A8	N1	A8		A5
Compliance of Lungs	N4	A2	N12	A4	N12	A3	N1	A5		A4
Work of Breathing at Rest	N4	A2	N10	A6	N7	A8		A6		A4

We have drawn the following inferences from these studies carried out in conjunction with the two research units:

1. In general, Sydney test results tend to conform to the Joint Coal Board grading, but as the range of normal values is wide, it would appear that considerable impairment is required of any one particular function of the lungs before it becomes measurable.

2. Patients with any grade of pneumoconiosis, or with early bronchitis, may give normal or abnormal results, although the more severe the lesion, the more likely are the results to be abnormal. Massive fibrosis may yield normal or abnormal results to all function tests.
3. Patients graded R0 normal or R1 slight disability by the Joint Coal Board have nearly always been normal when tested in Sydney, but may occasionally give a borderline or an abnormal result in one or more tests.
4. Patients graded R2, moderate disability, gave in Sydney mostly frankly abnormal, sometimes borderline, results.
5. Patients graded R3, moderately severe, or R4 severe disability, gave abnormal results on every occasion in Sydney; usually they showed abnormalities in all components of lung function.
6. Patients with massive fibrosis radiologically but who were clinically normal gave, on several occasions, normal results to every test except the work of breathing and pulmonary compliance. On the other hand, patients with severe bronchitis who gave other abnormal respiratory function tests were occasionally normal in their work of breathing and in pulmonary compliance.
7. Ventilatory and Lung Volume Measurements give early indication of disordered respiratory function in coalminers. This is to be expected as our patients present a mixed form of disease characterised initially by a disorder of the bellows mechanism, i.e. bronchospasm, loss of elasticity. Our spirometric results have been confirmed by similar ventilatory tests at the Hallstrom Institute and University.
8. The RV/TLC and DS/VT detected a large number of early cases; and the Physiological Shunt/Cardiac Output, Q.V.A./QT (venous admixture) also appears to be a very sensitive test.
9. Diffusion, Oxygen Saturation and Work of Breathing tests disclosed abnormal function, sometimes not detected clinically or spirometrically.

Therapy Studies

Over a three year period commencing in 1954 studies were carried out in an endeavour to determine the value of breathing exercises carried out under the supervision of trained physiotherapists, and of intermittent positive pressure breathing (using the Bennett valve) combined with application by aerosol methods of bronchodilators, vaso-constrictors, and detergents, in the treatment of the chronic respiratory diseases of miners.

By means of an examination comprising full medical and industrial history, clinical examination, postero-anterior chest X-ray, chest fluoroscopy, electrocardiogram and respirometer test, some 200 miners and ex-miners were selected as suffering from pneumoconiosis, emphysema, chronic spastic bronchitis, or some combination of these diseases, and free from other conditions with the exception in some cases of slight hypertension or uncomplicated atherosclerosis.

These men were given courses of treatment of standard duration and largely standard content, either physiotherapy or positive pressure breathing or a combination thereof, and during these courses no alteration was made to their current drug therapy. They had previously been studied intermittently, in many cases over years, and were all manifesting slow deterioration in health.

The results were assessed as subjective — improvement, no change, or worsening of ability to climb hills or walk on level ground — and objective — similar changes with respect to chest expansion, diaphragmatic excursus, presence of rhonchi and other physical signs, and performance in the spirometer tests (M.B.C. and T.V.C./1 sec.).

We concluded that supervised breathing exercises are almost universally helpful to these patients, whilst positive pressure breathing plays a valuable role in selected patients — those in whom reversible bronchial obstruction is a major feature of their disease, those with marked cyanosis, and those with severe disease and cor pulmonale, especially in the presence of superimposed respiratory episode.

Post Mortem Studies

Over the past 10 years we have accumulated some 360 heart-lung specimens of deceased mineworkers, of whom 262 were found to have some degree of pneumoconiosis and/or emphysema as a result of pathology studies, and 72 were considered to have died as the result of this disease or complications arising therefrom. Sixty have been studied by large lung section as well as histologically.

Separate systems of grading of extent of pneumoconiosis and emphysema in the pathological specimen have been adopted.

There have been found a partial correlation between the extent of pneumoconiosis and that of emphysema (usually focal in type); a good correlation between extent of pneumoconiosis and length of working life in the coal industry, and particularly at the coal face; and a relatively poor correlation between extent of emphysema and the occupational exposure.

We have also found that the ante mortem diagnosis of pneumoconiosis, inclusive of the very early stages, over the years has been found correct at post mortem in 80 per cent of cases (there being 5 per cent of false positive and 15 per cent of false

negative diagnoses). The order of accuracy is not greatly affected according to whether the last medical examination of which adequate records were available for study was carried out more than or less than five years before death.

On the other hand, there have been many false negative diagnoses in the case of emphysema where we can only claim correct ante mortem diagnosis in 50 per cent. Tying up with the known more rapid clinical course of pulmonary emphysema than of fibrosis, the order of accuracy improves, at the expense of the false negatives, to 66 per cent in the case of those men examined within two years before death. In recent years, since the introduction of the comprehensive medical examination routine referred to above, a degree of accuracy fairly comparable to that of pneumoconiosis has been achieved.

There have been very few false positive diagnoses of pulmonary emphysema.

SUMMARY

1. Pneumoconiosis of coalminers is an occupational disease entity which appears to be a conglomerate of fibrosis, emphysema, bronchial obstruction, and simple clogging of the lung tissues and air spaces with dust. In the later stages recurrent respiratory infections add further parenchymal and pleural fibrosis and aggravate the emphysema.

2. The prevalence of penumoconiosis and of chronic obstructive bronchitis and emphysema amongst New South Wales coalminers is discussed.

3. Respirometer tests of lung function in miners have been compared with more detailed laboratory studies and appear to have considerable value for use in field work amongst miners.

4. Systems of classification and grading of disease in use in New South Wales are described. They are useful for continuing studies in epidemiology and of the effectiveness of preventive measures, and can be used as a basis for compensation assessments.

5. Supervised breathing exercises and intermittent positive pressure oxygen breathing with aerosols have value in the treatment of these diseases.

6. Some results of post mortem studies are given.

RESUMEN

1. La neumoconiosis de los mineros de carbón es una enfermedad ocupacional que parece ser un conglomerado de fibrosis, enfisema, obstruction bronquial, y simple taponamiento de los tejidos pulmonares y de los espacios aéreos por el polvo. En los estados tardíos las infecciones respiratorias agregan más fibrosis parenquimatosa y pleural y agravan el enfisema.

2. La prevalescencia de la neumoconiosis y de bronquitis crónica obstructiva y del enfisema entre los mineros de carbón de Nueva Gales del Sur se estudia en este trabajo.

3. Las pruebas por respirómetro de la función pulmonar en los mineros, se han comparado con otras pruebas más detalladas de laboratorio y parecen tener valor considerable para el uso en el campo de trabajo entre los mineros.

4. Se describen los sistemas de clasificación y gradación de la enfermedad que se usan en Nueva Gales del Sur. Son útiles para estudios continuados sobre epidemiología y para estimar el valor de las medidas preventivas y pueden usarse como base para valuar las compensaciones.

5. Los ejercicios respiratorios vigilados y la administración de oxígeno a presión positiva intermitente con aerosoles, tienen valor para el tratamiento de estas enfermedades.

6. Se presentan algunos resultados de estudios postmortem.

RESUMÉ

1. La pneumoconiose des mineurs de charbon est une maladie professionnelle qui semble être un ensemble de fibrose, d'emphysème, d'obstruction bronchique et d'un simple empâtement des tissus pulmonaires et des espaces aériques par la poussière. Dans les dernières phases de l'évolution, des infections respiratoires récidivantes sont à l'origine d'une fibrose parenchymateuse et pleurale et aggravent l' emphysème.

2. L'auteur discute la preédominance de pneumoconiose et de bronchite chronique obstructiva avec emphysème chez les mineurs de charbon des Nouvelles Gales du Sud.

3 Des tests spirométriques de la fonction pulmonaire chez les mineurs ont été comparés avec des études de laboratoires plus détaillées. Ils semblent avoir une valeur considérable pour l'emploi dans le domaine de la médecine du travail des mineurs.

4. L'auteur expose les systèmes de classification et d'évaluation du degré de l'affection en usage dans les Nouvelles Gales du Sud. Ils sont nécessaires pour poursuivre les études d'épidémiologie et pour prendre des mesures préventives efficaces. Ils peuvent être utilisés comme base pour le taux des rentes.

5. Des exercices respiratoires contrôlés, et la respiration d'oxygène en pression positive intermittente avec des aérosols constituent un traitement valable de ces affections.

6. Quelques résultats d'études anatomo-pathologiques sont exposés.

ZUSAMMENFASSUNG

1. Die Pneumokoniose der Bergleute aus Kohlengruben ist eine Berufskrankheit; sie scheint ein Konglomerat von Fibrose, Emphysem, bronchialem Verschluss und einfache Verstopfung des Lungengewebes und der lufthaltigen Räume mit Staub ?????? In den weiter fortgeschrittenen Stadien fügen sich wiederholende Infektionen des Respirations-traktes eine weitere parenchymatöse und pleurale Fibrose hinzu und verschlechtern das Emphysem.

2. Diskussion über die Häufigkeit der Pneumokoniose und der chronischen Bronchitis mit Bronchusverschluss and des Emphysems bei den Bergleuten der Kohlengruben von von Neu Süd-Wales.

3. Lungenfunktionsprüfungen mit dem Gerät der Atembewegungen bei Bergleuten wurden mit mehr in das einzelne gehende Laboratoriumsuntersuchungen verglichen und scheinen von beträchtlichem Wert für den örtlichen Einsatz bei der Untersuchung von Bergleuten.

4. Beschreibung der in Neu Süd-Wales gebräuchlichen Arten der Klassifikation und Einreihung. Sie sind wertvoll für laufende Untersuchungen in epidemiologischer Hinsicht und bezüglich der Wirksamkeit von Verhütungsmassnahmen. Sie lassen sich anwenden als Grundlage für die Bemessung der Entschädigung.

5. Kontrollierte Atemübungen und intermittierende positive Sauerstoffdruckatmung mit Aerosol haben ihren Wert für die Behandlung dieser Krankheit.

6. Es werden einige Ergebnisse von Sektionsbefunden vorgelegt.

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The Incidence of Peptic Ulceration in Chronic Obstructive Pulmonary Emphysema

A Statistical Study

LOUIS ZASLY, M.D., F.C.C.P., GEORGE L. BAUM, M.D., F.C.C.P., and JOHN M. RUMBALL, M.D.
Coral Gables, Florida

An increased incidence of chronic peptic ulceration in patients with chronic obstructive pulmonary emphysema has been reported by several investigators.[1-5] Percentages have been stated to range from 19 to 42.8 (Table 1).

The frequency of chronic peptic ulcer in the general population has been estimated by life insurance statistics to be 3.7 per cent and by selective service examinations to be 3.3 to 4.3 per cent.[6] Ivy[7] et al., have stated that approximately 5 to 10 per cent of the adult population of the United States will have or have had ulcer symptoms during their life time, and that any annual survey may vary from 1 to 3 per cent.

Recently (1958) Flint and Warrack[1] analyzed 1124 autopsies over a two year period and found 87 cases of diffuse pulmonary emphysema. Of these 87, peptic ulcer was noted in 18 (21 per cent). The remaining 1037 cases without emphysema revealed 17 with peptic ulcer (1.6 per cent). In a separate analysis[1] of a different one year period, 88 consecutive patients dying of congestive heart failure showed 24 to have cor pulmonale. Of these 24 cases, 10 had peptic ulcer and of the 64 others, only three had this condition.

	No. of Pts.	No. of Pts. with Peptic Ulcer	Incidence %
Weber & Gregg[4]	70	30	42.8
Green & Dundee[5]	64	12	19.0
Lowell et al[6]	25	6	24.0
Latts et al[7]	479 107*	74 29	15.4 27.1
Plotkin[8]	65	21	32.0
Author's Series	478	109	22.7
* Indicates autopsy series			

TABLE I

Incidence of Peptic Ulcer in Pulmonary Emphysema

From the Medical Service, Veterans Administration Hospital and the Department of Medicine, University of Miami School of Medicine.

A statistical study of the prevalence of peptic ulcer associated with chronic pulmonary emphysema is herein presented.

Methods

Retrospective analyses of the records of 478 subjects hospitalized with a diagnosis of chronic pulmonary emphysema were made. These patients were admitted to the Veterans Administration Hospital, Coral Gables, Florida, from January 1, 1951 to December 31, 1956. The diagnosis in each instance was classified according to the certainty with which it could have been made.

Patients were classified as unequivocal chronic obstructive pulmonary emphysema when relevant histories and physical findings were corroborated by satisfactory fluoroscopic examination, pulmonary function measurements, or post-mortem examination.

Similar classifications were made whenever a diagnosis of peptic ulcer was entertained. Unequivocal peptic ulcer referred to confirmation by positive roentgen evaluation, operation, or post-mortem examination. A probable diagnosis was made when a definite ulcer history was associated with either upper gastrointestinal bleeding, high titratable gastric acidity, or suggestive radiographic findings. Possible peptic ulcer included those instances where relevant histories were not confirmed by roentgenographic findings, high gastric acidity, or peptic ulcer complications.

Controls consisted of 3225 patients of an identical age group (over 40) admitted to the same institution during the calendar year 1956. These were evaluated as to the presence or absence of chronic peptic ulcer. Unequivocal, probable, and possible designations were also applied to these ulcer cases. It was felt that the group age over 40 for the year 1956 was representative of the admissions for any of the years from 1950 to 1956, although seasonal variations in the character of admissions may have occurred. In the authors' opinion there is no reason to feel that criteria for admission varied materially from year to year. It is also recognized that selection of patients for admission with two co-

	Pulmonary Emphysema		Controls	
Peptic Ulcer	109	(22.7%)	86	(2.7%)
No Peptic Ulcer	369	(77.3%)	3139	(97.3%)
TOTALS	478		3225	
$P < .001$				
95% confidence interval - 16% to 24%				

TABLE II

Peptic Ulcer in Chronic Pulmonary Emphysema and in Control Group

existing diseases may exist over that for one disease. However, this factor may occur in any similar survey. For these reasons, the use of this control series was deemed to be justified.

Results

Of the 478 subjects diagnosed as chronic obstructive pulmonary emphysema, there was evidence of chronic peptic ulcer in 109 (22.7 per cent). This is contrasted with an incidence of 2.7 per cent in the control group (Table II). Of 208 patients classed as unequivocal pulmonary emphysema, there was evidence of chronic peptic ulcer in 61 (29.3 per cent) Table III. Of the entire group of 478 emphysematous subjects, 80 (16.7 per cent) demonstrated unequivocal evidence of chronic peptic ulcer, contrasting with an incidence of 1.7 per cent in the control group (Table IV). The incidence of unequivocal ulcer in the group with unequi-

	Unequivocal Pulmonary Emphysema	Controls
Peptic Ulcer	61 (29.3%)	86 (2.7%)
Not Peptic Ulcer	147	3139 (97.3%)
TOTALS	208	3225
P< .001 95% confidence interval - 20% to 33%		

TABLE III

Peptic Ulcer in Patients classed as unequivocal Pulmonary Emphysema and in Control Group

	Pulmonary Emphysema	Controls
Unequivocal Ulcer	80 (16.7%)	56 (1.7%)
Not Unequivocal Ulcer	398 (83.3%)	3169 (98.3%)
TOTALS	478	3225
P < .001 95% confidence interval - 12% to 18%		

TABLE IV

Incidence of Unequivocal Peptic Ulcer in Pulmonary Emphysema and in Control Group

vocal evidence of chronic obstructive pulmonary emphysema was 23.1 per cent (Table V). The percentages for the study group showed a statistically significant difference from that for the control group ($p<.001$).

Table VI is a summation of the incidence of chronic peptic ulcer in the 478 patients with chronic pulmonary emphysema. In addition to the 16.7 per cent with unequivocal ulcer, nine (1.9 per cent) were considered as probable ulcer cases, 20 (4.1 per cent) were placed in the possible category.

In 42 patients definite determination of the anatomical site of ulceration was made; 23 were duodenal and 19 were gastric.

	Unequivocal Pulmonary Emphysema		Controls	
Unequivocal Ulcer	48	(23.1%)	56	(1.7%)
Not Unequivocal Ulcer	160	(76.9%)	3169	(98.3%)
TOTALS	208		3225	
P<.001				
95% confidence intervals - 16% to 27%				

TABLE V

Incidence of Unequivocal Ulcer in Unequivocal Pulmonary Emphysema and in Control Group

Pulmonary Emphysema 478 Cases		
Peptic Ulcer	No.	%
Unequivocal	80	16.7
Probable	9	1.9
Possible	20	4.1
	109	22.7

TABLE VI

Peptic Ulcer in Chronic Pulmonary Emphysema, Author's Series

The hospital records of 46 subjects were considered adequate for analysis of time interval relationship. In 34, symptoms referable to pulmonary emphysema preceded those of ulcer by two to 32 years (mean = 14.8 years). Evidence of peptic ulcer anteceded those of the pulmonary disease by one to 21 years (mean = 10.4 years) in 12 patients.

Comment

An increased incidence of chronic peptic ulcer in chronic pulmonary emphysema has been demonstrated. A possible relationship between blood acid base balance and peptic ulcer was indicated by Nye and Sippe of Australia in a statistical study conducted in tropical and temperate climes. The increased incidence of hypochlorhydria in warmer areas was presumed to be related to lowering of plasma carbon dioxide as a result of constant hyperventilation.[9]

An increased incidence of peptic ulcer in the cooler parts of Australia has also been described.[10]

Increased gastric acidity incident to carbon dioxide inhalation has been demonstrated by Bakaltschule,[11] Apperly and Crabtree,[12] as well as Browne and Vineburg.[13] Kiefer[14] found that evalation of plasma carbon dioxide content by alkali administration was not associated with significant alteration in gastric secretions. In a separate study our unpublished data revealed no significant relationship between arterial carbon dioxide tension and gastric acidity in patients with chronic obstructive pulmonary emphysema.[15]

The almost equal incidence of duodenal and gastric ulcer is similar to that noted by Flint and Warrack.[8] This is of considerable interest in view of well-known marked increased incidence of duodenal over that of gastric ulcer.

Other factors that might be thought to influence the association of these two diseases are respiratory infections, cigarette smoking, stress, and tension. It is clear that no factor common to either of these apparently similar diseases has been established. Further investigations as to the cause or causes of this relationship are under way.

SUMMARY

A statistical study of hospitalized patients indicated a significantly increased incidence of chronic peptic ulcer in chronic obstructive pulmonary emphysema. Of 478 cases studied, 109 (22.7 per cent) had evidence of associated emphysema and peptic ulcer. A control group of 3225 patients of same age group without emphysema revealed an incidence of 2.7 per cent.

ACKNOWLEDGMENT: The authors express their appreciation to Iris Kiem, M.S., M.P.H. for her invaluable biostatistical analyses.

RESUMEN

Un estudio de enfermos hospitalizados revela un aumento de la frecuencia de la úlcera péptica crónica entre los enfermos con enfisema pulmonar obstructivo. De 478 casos estudiados, 109 (22.7 por ciento) tenían evidencia de úlcera péptica y enfisema.

Un grupo de control de 3,225 enfermos de la misma edad y sin enfisema reveló una frecuencia de 2.7 por ciento.

RESUMÉ

Une étude statistique des malades hospitalisés montra une augmentation considérable de la fréquence des ulcères gastriques dans l'emphysème pulmonaire obstructif chronique. Sur 478 observations, 109 (22.7%) firent la preuve d'une association d'emphysème et d'ulcère gastrique. Un groupe témoin de 3,225 malades du même âge sans emphysème révéla un taux de 2.7%.

ZUSAMMENFASSUNG

Eine statistische Untersuchung an Krankenhaus-Patienten ergab ein beträchtlich häufigeres Vorkommen von chronischen peptischen Magengeschwür bei chronischem obstruktiven Lungenemphysem. Unter 478 untersuchten Fällen hatten 109 (22.7%) Anzeichen für ein gemeinsames Bestehen von Emphysem und peptischem Geschwür. Eine Vergleichsgruppe von 3225 Patienten der gleichen altersstufe ohne ein E hysem ergab eine Häufigkeit von 2.7%.

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Program of Tuberculosis Control Among University Students

Survey of Results for the First 14 Years of Operation

FERNANDO D. GÓMEZ, F.C.C.P., C. EPIFANIO, M.D., and M. MELLO AGUERRE, M.D.*
Montevideo, Uruguay

In 1939[1] one of us (Gomez) highly concerned with the frequency at which tuberculosis affected medical students, undertook a tuberculin and photoroentgen survey among them.

In 1942 a compulsory free-of-charge six-monthly tuberculin and roentgenologic examination was set up for all students of medicine and obstetrics.

Finally, at the beginning of 1945 this prophylactic program was made extensive, on a yearly basis, to all of the students attending the Schools under the University of Montevideo. The number of screened undergraduates for all the Schools totalled 17,259.

The control program under discussion is in charge of the "Dispensario Profilactico Universitario" (D.P.U.), inaugurated in 1942 as a dependency of the Institute of Pneumology and Chair of Pneumological Clinic of the School of Medicine.

In order to secure, on the part of the students, the regular compliance with periodical screenings, applications for enrollment or examinations must be accompanied by the D.P.U. card brought to date.

The D.P.U. staff is made up of a phthisiologist specialized in the interpretation of roentgenograms, a social worker, and two assistants who perform and read tuberculin tests, take and develop routine photoroentgens as well as a first roentgenography of those presenting abnormalities.

Once the presence of a lesion is confirmed, all the clinical, radiological and laboratory studies, as deemed necessary for a correct diagnosis, are conducted. Those found sick are given adequate advice conducive to better treatment. The physician in charge of D.P.U. renders them free-of-charge professional service in his own office, at their homes or else provides for hospitalization, according to the nature of the process disclosed and to the economical or social status of the concerned individuals. In Uruguay, education is free-of-charge at all levels. There are no special institutions for the treatment of tuberculous students. The choice of physician and treatments are entirely optional; there are no regulations compelling the sick undergraduate to discontinue his studies temporarily or definitely or to undergo an adequate treatment.

Material and Methods

When first filed at D.P.U., a brief clinical history of the student is taken including personal data: age, sex, civil status, nationality, domicile, courses being followed and whether he works simultaneously. If the latter is the case, hours and nature of occupation are recorded. He is questioned as regards family and personal health background, with

*From the Instituto de Neumología y Cátedra de Clínica Neumológica de la Facultad de Medicina.

special emphasis on tuberculosis and diseases of the respiratory system. The enquiry likewise comprises information concerning any previous prophylactic examinations and BCG vaccination. During subsequent six-monthly or yearly calls, he is questioned as to any novel developments in order to bring his record up to date. Interviews are at all times strictly private.

Once his record is completed the student moves on to an adjoining room where he is given a Pirquet tuberculin test with synthetic old tuberculin (SOT), by means of the Stewart-Trambusti cutaneous puncture technique. Through two drops of tuberculin placed 5-10 cm. away from each other, on the flexion face of the disinfected forearm, two punctures are made with a sterilized pin.

Every papule at least 3 mm. in diameter within 48-72 hours is considered positive. Results are recorded in millimeters, by calculating the main diameter of both reactions. Negatives are now made a Mantoux reaction with 100 TU (1 mg. SOT). A positive interpretation is given to papules at least 10 mm. in diameter within 48-72 hours. Those still tuberculin negatives are then submitted to new intradermal reaction with 1000 TU (10 mg. SOT). At the same time two additional Stewart-Trambusti reactions are performed on the opposite forearm through the same number of drops of a fresh 10 per cent BCG emulsion, with a few centimeters separation between them. This test is designed to investigate latent or infratuberculin allergy. The Mantoux reaction and the two cutaneous punctures with BCG are read on the 4th or 5th day. The former is interpreted in accordance with the above standards; the latter are regarded as positive when they set up a red papule irrespective of diameter. This simultaneous investigation of infratuberculin allergy enables testers to rule out as unspecific all those 10 mg. SOT positive Mantoux tests unaccompanied by likewise infratuberculin positive reactions. In those found tuberculin negative, the BCG test discriminates between those who have lost hypersensitivity to tuberculin and noninfected individuals. The proportion of tuberculin-negatives with 100 and 1000 TU, carriers of infratuberculin allergy was 33.3 per cent. The percentage of tuberculin negatives with only 100 TU but positive with 1000 TU brings up the rate of infratuberculin reactors among students to 73.5 per cent.[2]

On the day the tuberculin investigation is conducted, a chest photoroentgen is taken as well. An automatic unit for 70 mm. film is utilized. The definite results of these examinations are recorded on a card which testifies to the bearer's periodical calls at D.P.U. When the student is found diseased only a "checked up" entry is recorded, the results of all the investigations being handed to him separately, thereby precluding any embarrassment when the presentation of the card is required of him.

For those found tuberculin-negative vaccination by ingestion of 20 centigrams of fresh BCG in one single dose is advised.

Tuberculin tests are repeated yearly, even with tuberculin-positives, in order to ascertain modifications in the level of cutaneous sensitiveness to tuberculin. We ascribe a poor prognosis to hyperergia not imputable to constitutional factors, for we believe it to reflect repeated contagion or weakening of biologic defenses and hence a propensity to falling sick

TABLE 1 — TUBERCULIN POSITIVES ACCORDING TO TYPE OF REACTION
Comparison of percentage with Pirquet and Mantoux

Age Years	TUBERCULIN POSITIVES MEN Pirquet %	MEN Mantoux %	MEN Increase %	WOMEN Pirquet %	WOMEN Mantoux %	WOMEN Increase %	TOTAL Pirquet %	TOTAL Mantoux %	TOTAL Increase %
15-19	47.5	79.0	39.9	39.1	72.9	46.4	44.5	76.8	42.1
20-24	59.7	83.4	28.4	48.1	78.3	38.6	56.0	81.8	31.5
25-29	77.1	92.3	16.5	63.3	85.0	25.5	73.5	90.4	18.7
30 & +	86.9	96.2	9.7	68.4	91.0	24.8	82.3	95.0	13.4
Total	61.2	84.6	27.7	48.0	78.1	38.5	57.0	82.5	30.9

for which reason hyperergic students are directed to repeat the photoroentgen every three months during that year.

Results

Between early 1942 and December 31, 1955, 17,259 students were examined at the D.P.U. The surveyed group was made up of 69.3 per cent males and 31.7 per cent females. At their first visit 30.6 per cent were aged between 15 and 19; 47.5 per cent between 20 and 24 years; 13.8 per cent between 25 and 29 and 8.1 per cent, 30 or over.

The percentage of negatives — by the first test — who became positive with 100 or 1000 TU declined for both sexes with age.

The number of examinations performed upon the same person throughout follow-up by the D.P.U. ranged between 1 and 27. The total of x-rays for the 17,259 undergraduates was 76,535 (53,535 males and 23,000 females). The 13,007 students with two or more examinations totalled 50,102 persons-year; the average follow-up time was as of December 31, 1955, 3.8 years and the number of examinations for each, 5.5.

TABLE 2 — TUBERCULIN ALLERGY UPON ENROLLMENT ON DIFFERENT PERIODS
Percentage results of Pirquet and Mantoux reactions according to age and sex

Age Years	Performed	Proportion of tuberculin positives MALE 1942-46 %	MALE 1947-51 %	MALE 1952-55 %	FEMALES 1942-46 %	FEMALES 1947-51 %	FEMALES 1952-55 %
15-19	Pirquet	51.0	48.5	45.0	44.6	40.9	35.6
	Mantoux	78.6	76.9	81.0	75.4	66.2	77.1
20-24	Pirquet	62.1	61.1	54.7	50.9	46.5	46.5
	Mantoux	84.8	82.0	83.0	79.1	76.1	79.4
25-29	Pirquet	77.0	78.9	75.7	64.4	60.2	61.9
	Mantoux	92.3	90.5	94.1	86.6	75.7	87.6
30 and	Pirquet	85.7	92.3	86.0	66.2	73.7	73.9
+	Mantoux	96.5	95.6	95.6	91.5	90.8	89.1
	Pirquet	67.5	59.9	53.7	54.2	46.2	42.8
TOTAL	Mantoux	87.4	81.6	83.6	81.4	72.6	79.0
	Increase %	22.8	26.6	35.8	33.4	36.4	45.8

TUBERCULIN POSITIVES
Total for both sexes

	1942-46	1947-51	1952-55
Pirquet	63.6%	55.6%	49.9%
Mantoux	85.6%	78.8%	82.0%
Increase with Mantoux	25.7%	29.4%	39.1%

TABLE 3—TUBERCULOUS INCIDENCE IN STUDENTS
According to age and type for persons-years

Age Years	PREVALENCE No. of Persons	Total Cases	°/°°	Persons-Year	INCIDENCE Total Cases	°/°°	Inapparent Cases	°/°°	Acute Cases	°/°°
15-19	5,295	23	4.3	15,548	56	3.6	24	1.5	32	2.1
20-24	8,219	46	5.6	25,332	107	4.2	53	2.1	54	2.1
25-29	2,374	20	8.4	6,103	19	3.1	11	1.8	8	1.3
30 and +	1,371	7	5.1	3,119	11	3.5	8	2.6	3	1.0
Total	17,259	96	5.6	50,102	193	3.9	96	1.9	97	1.9

Twenty-four and six-tenths per cent of the surveyed group had only one single photoroentgen taken, 55.8 per cent between 2 and 6; 18.1 per cent between 7 and 18 and 1.5 per cent between 23 and 27. Hence the average for most individuals (55.8 per cent) is of 2 to 6 examinations. The duration of the University curriculum is about 6 years, but the longest careers average 7 and even more years.

Disclosures of unknown cases embodying the yield of the systematic photofluoroscopic screening (unknown prevalence) comprises a total of 60 cases, of which 32 (2.7 per thousand) were males and 28 (4.9 per thousand females).

Throughout the period under consideration (1942-1955) the incidence totalled 193 processes, 137 in men and 56 in women. Of these 193 active cases, 96 (5.5 per thousand) correspond to inapparent lesions diagnosed by systematic examination and 97 (5.5 per thousand) were disclosures of acute symptomatic forms between two mass surveys in persons found normal weeks or months earlier, during the systematic periodic control.

By sex, 73 (6.0 per thousand) lesions of intercurrent incidence and 64 (5.4 per thousand) of inapparent incidence were seen in men and 24 (4.2 per cent) and 32 (5.6 per cent) in women.

The overall tuberculosis morbidity was of 289 processes (16.7 per cent) among the 17,259 students followed-up over an average 3.8 year period.

During the 1942-47 period, 52.9 per cent of the incidence was of the intercurrent type, to decline down to 38.9 per cent in 1948-53.

The pulmonary forms are shown grouped according to the standard classification of the National Tuberculosis Association. The moderately advanced and the far advanced are placed within one single group, for only one case, under therapeutic pneumothorax upon enrollment — presented a far advanced form with a cavern.

One of the above mentioned pleurisies actually corresponded to a polyserositis with Pott's disease. Two of the pulmonary lesions moreover

TABLE 4—ACCUMULATED TUBERCULOSIS INCIDENCE
According to periods; total until 31-XII-57
and during first 4 years following enrollment

Year of incorporation to control	Number of students	YEARLY RATE OF ONSET TOTAL Cases	%	IN 4 YEARS Cases	%
1943-1945	3,793	78	2.1	57	1.5
1946-1948	3,848	47	1.2	37	1.0
1949-1951	3,251	20	0.6	17	0.5
1952-1954	3,897	7	0.2	—	0.0
Total	14,789	152	1.0	111	0.7

TABLE 5—TUBERCULOSIS MORBIDITY ACCORDING TO AGE AND TYPE OF LESION

Number of students: 17,259; active processes: 289; morbidity: 16.7%

Age Years	Pleurisy* Cases	*/**	Lymph-node pulmonary Cases	*/**	PULMONARY Minimal Cases	*/**	Advanced Without cavity Cases	*/**	Advanced With cavity Cases	*/**	Total Cases	*/**
15-19	14	2.6	11	2.1	27	5.1	7	1.3	20	3.8	54	24.3
20-24	18	2.2	19	2.3	60	7.3	27	3.3	29	3.5	116	52.3
25-29	3	1.3	2	0.8	16	6.8	4	1.7	14	5.9	34	15.3
30 and +	0	0.0	0	0.0	4	2.9	5	3.6	9	6.6	18	8.1
Total	35	2.0	32	1.9	107	6.2	43	2.5	72	4.2	222	
	12.1%		11.1%		37.0%		14.9%		24.9%		100.0%	

*Serofibrinous in all but one

presented, one an epididymo-orchitis and another a perianal abscess. One student, not computed within the former table, showed a renal tuberculosis without any other recognizable localization. One fourth (24.9 per cent) of all cases and 32.4 per cent of those with pulmonary tuberculosis presented cavities at the first examination.

A striking feature of the survey under consideration is that, despite the periodical check-up, advanced forms were present almost as frequently as minimal (1.5 o/oo for minimal forms and 1.3 o/oo for the advanced). This finding testifies to the fact that the severity of pulmonary processes at diagnosis is dependent on their evolutive potentiality rather than on the earliness of diagnosis.

In 204 of 289 diagnosed tuberculous cases, bacteriological diagnosis from sputa, gastric contents or pharynx smears, (direct examination and culture) was conducted. The rate of positive findings was 39.2 per cent and that of negatives, 60.8 per cent. The highest index of positive find-

TABLE 6—TUBERCULOSIS INCIDENCE ACCORDING TO AGE AND TYPE OF LESION

Persons-year observation: 50,102; number of incidence lesions: 193

Age Years	Pleurisies Cases	*/**	Lymph node-pulmonary Cases	*/**	PULMONARY Minimal Cases	*/**	Advanced Cases	*/**	Total Cases	*/**
15-19	13	0.8	7	0.4	19	1.2	17	1.1	36	2.3
20-24	16	0.6	14	0.6	45	1.8	32	1.3	77	3.0
25-29	2	0.3	1	0.2	7	1:1	9	1.5	16	2.6
30 and +	0	0.0	0	0.0	2	0.6	9	2.9	11	3.5
Total	31	0.6	22	0.4	73	1.5	67	1.3	140	2.8

TABLE 7—TUBERCULIN ALLERGY UPON ENROLMENT AND TYPE OF LESION

Tuberculin Reaction	Pleurisy Cases	%	Lymph-node pulmonary Cases	%	PULMONARY Minimal Cases	%	Advanced Without cavity Cases	%	Advanced With cavity Cases	%	Total Cases	%
Negative (3.026) persons	6	2.0	14	4.6	7	2.3	1	0.3	3	1.0	31	10.2
Stewart-Trambusti positive (9.841) persons	18	1.8	16	1.6	87	8.8	36	3.7	54	5.5	211	21.4
Mantoux positive (4.392) persons	11	2.5	2	0.5	13	3.0	6	1.4	15	3.5	47	10.7

ings (44.6 per cent), corresponded to cases of acute intercurrent incidence and the lowest to those inapparent incidence (31.0 per cent).

In over half the cases (153, i.e., 52.9 per cent) treatment consisted only in an increase of hours of rest and improved diet. Most undergraduates carried on with their studies and when instructed to interrupt them it was only for a few months' time.

Therapeutic pneumothorax was instituted in 39 (13.5 per cent) cases, in 12 (4.2 per cent) associated with antibiotics or drug therapy. In 97 (33.6 per cent) the new drugs were utilized alone. A phrenicectomy was performed in one case.

As a rule, both collapse therapy and drugs were resorted to on recurrence or relapse, rather than as initial therapy. Once again it should be recalled that students were treated by physicians of their choice and that no regulations provide for the discontinuance of studies or submittal to treatment. Only periodical control is compulsory to those enrolling for courses or examinations.

Despite the irregular characteristics of the treatment, by December 31, 1955, 83.7 per cent (242 cases) presented a state of clinical cure. It is worth recalling that, at least once a year, the visiting nurse tries to contact all tuberculosis cases diagnosed while taking university courses in order to request them to renew their examinations and question them about any fresh developments connected with their disease.

The average follow-up time of each of those found diseased was 73.1 months at the above date. For the 267 cases followed up for over a year the foregoing period was 78.7 months and for 44.7 of the total number, it ranged between 7 years and 13 years.

The group of improved cases composed of tuberculous students recently diagnosed or of those who had in most instances suffered relapse shortly before, totalled 25 (8.7 per cent), those stationary, 15 (5.2 per cent); one had worsened and 6 had died.

Of the latter, three had of tuberculosis before the advent of the new drugs (2 or caseous bronchopneumonia and 1 of military tuberculosis involving meningitis). The other 3 were in a state of clinical cure, their death being due to suicide, cardiac failure and acute adrenalitis, respectively.

Discussion

The present paper surveys the overall results of the control program of tuberculosis set up at the University of Montevideo over the 14 first years of operation.

BCG vaccination has been practiced in Uruguay since 1927. In 1940 its application was stepped up for newborns and in 1948 for tuberculin reactors of all ages. In August 1957 the "Comision Honoraria para la Lucha Antituberculosa"[6] started the systematic periodical tuberculin survey and photoroentgen mass screening of all the country's population together with BCG vaccination by mouth of all those found negative with Stewart-Trambusti reaction. The favorable response of the general population to this prophylactic campaign has deprived positive tuberculin reactions of their significance as criteria of virulent infection. Furthermore the lower intensity and habitually shorter duration of allergy produced by BCG would account for the high rate and sustained increase in the number of low reactors. We regard as such all those tuberculin negatives with the Stewart-Trambusti test who reacted positively to Mantoux with 100 or 1000 TU.

Between 1942-46 and 1952-55 the proportion of positive cutaneous tests declined by 21.5 per cent. Nevertheless, the overall rate of positives dropped by a bare 4.2 per cent owing to the increase in number of low-reactors.

While we believe BCG vaccination explains satisfactorily the observed phenomenon, we cannot rule out the possibility that a gradual increase of low-reactors may in part be indicative of the de-tuberculization stage this country is currently undergoing as

reflected by the steep drop in tuberculosis mortality. Another expression of this epidemiologic period is the high proportion of latent or infratuberculinic reactions encountered.

In 1950,[2] in the course of a survey conducted among undergraduates, we found that 33.3 per cent of tuberculin negatives investigated with up to 1000 TU reacted positively to the BCG test. If, as admitted by most authors, the investigation of tuberculin allergy is carried no further than the 100 TU level in order to avoid the frequent development of unspecific reactions ascribed to the 1000 TU test, the proportion of tuberculin negatives favorably reacting to the BCG test, reaches 73.5 per cent. This proves that less than 10 years ago three-quarters of tuberculin negatives between the ages of 20 and 25 corresponded to persons infected with the tubercle bacillus who did not react to tuberculin. Incidentally, medical students presented for whatever age group a higher index of tuberculin positives than those of other Schools.

The unknown prevalence brought out by the mass survey was 3.5 per thousand. In medical students the index was 2.9 o/oo.

Among the 50,102 followed-up persons-year, the 193 tuberculous lesions disclosed following a previously normal photoroentgen represent a 3.9 o/oo incidence. This rate is by no means the actual yield of the mass screening, since the survey disclosed only 96 processes unknown to their carriers. The inapparent 1.9 o/oo incidence referred to was identical to the intercurrent symptomatic index elicitable between two systematic mass examinations, totaling 97 cases, i.e., 1.9 per thousand. The intercurrent incidence progressively decreased with time. During the 1942-47 period it represented 52.9 per cent of the total; in 1948-55 it dropped down to 38.9 per cent.

Medical students totallized 18,190 persons-year under control with a 5.8 o/oo incidence, that is, nearly by one-third higher. Among them the intercurrent acute onset was 40.6 per cent higher than for the remaining students. According to our experience (7-8) and that of other authors, acute incidence lesions involve an increased evolutive potential and greater initial severity. Unlike inapparent lesions, when neglected and not treated early, they are likely to worsen within a few months' lapse.

Out of the 289 cases of active tuberculosis diagnosed among the 17,259 students between 1942 and the end of 1955, 156, that is, slightly over half — to be precise — 53.9 per cent — were brought out by systematic radiophotographic screening.

The remaining 46.1 per cent were so as a result of spontaneous consultation, owing to their feeling sick. This factor considerably reduces the significance of the systematic control set up, although it cannot be denied that by focussing public attention on the tuberculosis problem the mass screening project has given rise to a genuine awareness as far as early diagnosis is concerned.

It is of interest to observe that in the course of time a progressive drop of morbidity and the disappearance of tuberculosis mortality among the group under consideration, has taken place.

The morbidity declined from 1.5 per cent throughout the 4 years following enrollment of those filed between 1943 and 1945, to 1.0 per cent for students enrolled between 1946 and 1948, 0.5 per cent for those joining in 1949-51, down to an ultimate 0.0 for those who did so in 1952-54.

The question arises as to whether the above decrease is to be regarded as a direct result of the established control program or else mostly due to a favorable spontaneous evolution of tuberculous morbimortality among the population at large, in conjunction with direct and indirect factors incident to the antituberculosis fight.

Notwithstanding the narrow age span of the group considered, it is found that pleural and lymph node-pulmonary forms have been prevalent among the youngest students. Excavated lesions predominated among senior undergraduates.

As time passed by, lymph node-pulmonary forms became apparent mainly in those who were tuberculin negatives at the beginning; minimal pulmonary forms, as well as advanced forms with cavities were predominantly found in those who originally were positive to the Stewart-Trambusti test.

Attention is called to the favorable evolution of the disease notwithstanding the fact that 24.9 per cent of the total incidence corresponded to lesions which were seen excavated upon diagnosis and that in many cases no active therapeutic measures were instituted except in those instances with a tendency toward progression, or in the presence of relapse. The three recorded deaths occurred prior to the advent of the new drugs.

Tuberculosis mortality rate was 0.06 0/00 persons-year. Lethality was as high as 1.0 per cent. No student had to give up his studies owing to tuberculosis; very few were forced to interrupt courses for several months in order to take a prescribed rest.

The set-up for six-monthly or yearly check-ups is at first sight inconsistent with the high proportion (24.9 per cent) of advanced lesions and the disclosure of cavities during the first examination. Hence the above findings indicate that we are concerned with a group possessing low organic resistance frequently handicapped by inadequate living standards. With such a background, repeated systematic examinations are hardly ever conducive to the diagnosis of minimal lesions. This lowering of organic resistance is the usual cause of intercurrent forms of acute onset, characterized by their higher evolutive potential.

From the above survey it is readily inferable that the tuberculosis problem among university students has, to a large extent, lost importance throughout the period

covered by this study. Since a trend has been observed over the last decade as regards the popula[illegible]e question arises as to what degree did the program dealt with, influ[illegible]e present favorable status.

SUMMARY

A survey is made of results attained as of December 1955 in conjunction with a tuberculosis control program set up for University students in 1942, comprising compulsory, periodical, free-of-charge tuberculin and photoroentgen examinations.

The analyzed group is made up of 17,259 undergraduates, of which 57.0 per cent proved tuberculin positives with the Stewart-Trambusti test. This percentage rose to 82.5 per cent on submitting tuberculin negatives to intradermal reaction with 1 mg., and when necessary 10 mg. SOT. In the course of time a gradual increase of low reactors was found.

The average number of examinations per person was 5.5 while follow-up totalled 3.8 years.

Tuberculosis prevalence was 5.6 per thousand, made up of 36 processes known by the concerned individuals, and 60 unknown inapparent lesions.

Among the 50,102 person-years under observation, the incidence was 3.9 per thousand. This comprises 96 inapparent tuberculous lesions brought out by the systematic photoroentgen examination and 97 acute intercurrent cases appearing between two systematic examinations in those found normal.

The incidence throughout the four years following the intial control, gradually declined with time, passing from 1.5 per cent for students enrolling between 1943 and 1945 down to 0.0 per cent for those filed in 1952-54.

Of the total number of tuberculosis diagnosed, 24.9 per cent were advanced processes with cavities.

In tuberculin negatives and low reactors, tuberculosis incidence was slightly over 10 per thousand, while in positives by the Stewart-Trambusti test it was over 21 per thousand.

83.7 per cent of the cases presented a state of clinical cure by December 31st, 1955 (average follow-up: 73.1 months).

Three students had died of tuberculosis, all of them prior to the advent of antibiotics. The death rate was 0.06 per thousand persons-year.

RESUMEN

Se analizan los resultados alcanzados hasta diciembre de 1955 por un programa de control de la tuberculosis, establecido para los estudiantes universitarios desde el año 1942. El examen periódico, tuberculínico y radiofotográfico es obligatorio, anual y gratuito.

La muestra analizada comprende 17,259 estudiantes. El 57.0 por ciento se mostró tuberculinopositivo con la prueba de Stewart-Trambusti. La proporción se elevó a 82.5 por ciento al someter a los tuberculinopositivos a la intradermorreacción con 1 mg. y, cuando fué necesario, con 10 mg. de SOT. En el curso del tiempo se comprobó un aumento gradual de la proporción de hipoérgicos.

El promedio de exámenes por persona es de 5.5 y el de años de vigilancia de 3.8.

La prevalencia tuberculosa es de 5.6 por mil, integrada por 16 procesos conocidos por los interesados y 60 inaparentes, desconocidos. En las 50,102 personas-año bajo observación, la incidencia fué de 3.9 por mil. Comprende 96 tuberculosis inaparentes, descubiertas por el examen radiofotográfico sistemático, y 97 agudas intercurrentes, aparecidas entre dos exámenes de rutina, en encontrados normales.

La incidencia en los cuatro años inmediatos al ingreso al control, disminuyó gradualmente en el curso del tiempo, pasando de 1.5 por ciento para los alumnos inscriptos entre 1943-45, a 0.0 por ciento para quienes lo hicieron en 1952-54.

El 24.9 por ciento de todas las tuberculosis diagnosticadas, correspondieron a procesos avanzados con cavernas.

En los tuberculinonegativos y en los hipoérgicos, la incidencia tuberculosa fué ligeramente superior a 10 por mil, en los positivos por la reacción de Stewart-Trambusti fué mayor del 21 por mil.

El 83.7 por ciento se encontraba en estado de cura clínica el 31 de diciembre de 1955 (tiempo promedio de vigilancia: 73.1 meses).

Habían muerto 3 por tuberculosis; todos antes del advenimiento de los antibióticos. La mortalidad fué de 0.06 por mil personas-año.

RESUMÉ

L'auteur présente les résultats obtenus en décembre 1955, à la suite d'un programme de contrôle de la tuberculose à l'université, datant de 1942 et comprenant les examens tuberculiniques et radiologiques périodiques obligatoires et gratuits.

La groupe étudié est composé de 17,259 étudiants en cours de scolarité, dont 52% avaient des réactions tuberculiniques positives avec le test Stewart-Trambusti. Ce pourcentage atteint 82.5% lorsqu'on soumet les tests négatifs à l'intra-dermo-réaction avec 1 mmg. et si c'est nécessaire 10 mmg. de "S.O.T." Dans cette période on trouva une augmentation progressive des individus réagissant peu à la tuberculine. Le nombre moyen d'examens par personne fut 5,5 tandis que le contrôle totalisait 3,8 années.

La fréquence de la tuberculose fut de 5,6 pour mille, composée de 36 évolutions connues par les individus atteints et 60 lésions inapparentes et inconnues.

Parmi les 50,102 personnes-années sous observation, la fréquence fut de 3,9 pour mille. Ceci comprend 96 lésions tuberculeuses inapparentes, mises en évidence par la radiophotographie systématique et 97 cas aigus intercurrents, apparaissant entre deux examens systématiques chez les individus normaux.

Le taux pour les quatre années suivant le contrôle initial, déclina progressivement avec le temps, passant de 1,5% pour les étudiants ayant été contrôlés entre 1943 et 1945 à 0% pour ceux contrôlés en 1952-54.

Sur el nombre total de tuberculoses diagnostiquées, 24,9% étaient des cas sérieux avec cavités.

Chez les individus porteurs de réactions tuberculiniques négatives ou faibles, le taux de tuberculose fut légèrement au-dessus de 10 pour mille, tandis que pour les porteurs de réactions positives avec le test de Stewart-Trambusti il fut de plus de 21 pour mille.

83,7% des cas présentèrent un état de guérison clinique au 31 décembre 1955 (moyenne du tmps d'observation: 73,1 mois).

Trois étudiants moururent de tuberculose, tous avant l'avènement des antibiotiques. Le taux de mortal ité fut de 0,06 pour mille personnes et par an.

ZUSAMMENFASSUNG

Es wurde eine Übersicht vorgenommen von bis zum Dezember 1955 erreichten Resultaten in Zusammenhang mit einer Tuberkulose — Bekämpfungsaktion, die 1942 für Studenten der Universität aufgestellt worden war; sie umfasste obligatorische, periodische unentgeltliche Tuberkulinuntersuchungen und Röntgenaufnahmen.

Die analysierte Gruppe setzte sich zusammen aus 17259 nichtgraduierten Studierenden, von denen sich 57,0% als tuberkulinpositiv erwiesen (nach dem Stewart-Trambusti-Test). Dieser Prozentsatz stieg bis auf 82,5 %, nach dem die tuberkulin-negativen Fälle mit intrakutanen Reaktionen mit 1 mg und, falls erforderlich, mit 10 mg SOT. unterzogen worden waren. Im Laufe der Jahre fand sich ein schrittweiser Anstieg der schwach reagierenden Fälle. Die durchschnittliche Zahl der untersuchungen pro Person betrug 5,5 während sich die Verlaufsbeobachtungen auf insgesamt 3,8 Jahre beliefen. Die Häufigkeit an Tuberkulosefällen lag bei 5,6 auf 1000 und setzte sich zusammen aus 36 den betreffenden Individuen bekannten Prozessen und aus 60 unbekannten, verborgenen Befunden.

Bei den 50102 Personen-Jahren in laufender Beobachtung war die Häufigkeit 3,9 auf 1000. Hierzu gehörten 96 verborgene Tuberkulose-Befunde, die sich durch die systematische Röntgenaufnahme ergaben, und 97 akute, swischenzeitlich auftretende Fälle, die bei den als normal befundenen zwischen 2 systematischen Untersuchungen vorkamen.

Die Häufigkeit im Verlauf der 4 Jahre anschliessend an die einleitende Kontrolle fiel im Lauf der Zeit allmählich ab und war von 1,5 % für Studenten, die zwischen 1943 und 1945 inscrizierten, bis auf 0,0% bei denjenigen, die sich 1952 bis 1954 anmeldeten. Unter der Gesamtzahl der festgestellten Tuberkulose-Fälle befanden sich 24,9% mit fortgeschrittenen cavernösen Prozessen.

Bei Personen mit negativer und schwach positiver Tuberkulinreaktion lag die Tuberkulosehäufigkeit bei etwas über 10 auf 1000 während sie bei den mit dem Stewart-Trambusti-Test positiven Fällen mehr als 21 auf 1000 betrug.

83,7% der Krankheitsfälle boten das Bild einer klinischen Heilung zum 31.12. 1955 (durchschnittliche Kontrolldauer 73,1 Monate).

3 Studenten waren an ihrer Tuberkulose gestorben, sämtlich vor der antibiotischen Ära; das bedeutet eine Mortalität von 0,06 auf 1000 Personen-Jahre.

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SECTION ON CARDIOVASCULAR DISEASES

Optimism in Cardiovascular Disease*

JOHN FRANCIS BRIGGS, M.D., F.C.C.P.**
St. Paul, Minnesota

I deeply appreciate the privilege of giving this THE LOUIS MARK LECTURE. Those of us who knew Louis Mark well and had the good fortune of being associated with him intimately in his professional and personal life have recognized his great contributions to the science of diseases of the chest. He was not only an internationally known physician, but also internationally known for his abilities and talents in other fields such as organizational work, his philanthropies and, above all, his excellency at bridge which led to his becoming the national champion. No one ever turned to Louis Mark for counsel and guidance without receiving it in full measure. His own personal interest in the problems of his friends and his associates often led to the resolution of these problems quickly and efficiently. He and his wife, Fanny, lived together in a most Utopian ideal of personal relations. His passing brought, I am sure, as much sorrow to those of us whom he had adopted as it did those of his own family.

One of his great concerns in the professional field of medicine was the fragmentation of medicine into specialties and the splintering of these specialties into smaller disciplines and groups. He envisioned the time when the College of Chest Physicians would, within its walls, offer a common meeting ground for all these skills, talents and disciplines, all of the philosophies of basic science, as well as clinical and basic research. With a common ground, each of the fragments contributing its special knowledge would fall together so that the completed picture would bring greater hope for all humanity. Our College could, as a result of the union of these diversified groups, bring greater help to the victims of chest diseases. We greatly regret that our good friend and co-worker, Louis Mark, did not live to see his vision become a reality.

A union of talents, diversified as they may be, has brought optimism to the victims of cardiovascular disease. Through the joint efforts of the voluntary and the tax-supported health agencies, the philanthropic groups, private funds and foundations in conjunction with our public health agencies, heart disease is being conquered. Because of the contributions of the basic scientist, the pure researcher, the family physician, the clinical physiologist and pathologist, the biological chemist along with the clinical researcher in the various specialties of medicine, the cardiovascular patient can look to the future with greater anticipation and even hope for a cure.

*Fourth Annual Louis Mark Lecture, presented at the 25th Annual Meeting, American College of Chest Physicians, Atlantic City, June 3-7, 1959.
**Associate Professor of Clinical Medicine, University of Minnesota.

Witness with me, if you will, the tremendous advances made by the surgical groups interested in cardiovascular disease. Today we cure patent ductus arteriosis, coarctation of the aorta, the vascular ring syndromes, the aorta-pulmonary window syndromes. If we cannot cure, certainly we can offer palliation to the victim of vascular aneurysm whether acquired or congenital. We can often cure or palliate the victims of vascular thrombolic phenomena and the victims of closure and narrowing of the peripheral blood vessels. The congenital heart lesions such as pulmonary stenosis are now curable. The interatrial septal defects as well as the interventricular septal defects are also curable. At this time, we can palliate the victims of the tedrads. I think, however, that the future will bring to those patients a definitive cure. Many of the problems arising from the abnormal entrance of the great vessels are now being cured or palliated. The tricuspid stenosis of congenital origin lends itself to palliation by surgery, and certainly, we have demonstrated palliation of the acquired valvular defects in mitral stenosis and aortic insufficiency. The future holds hope for victims of mitral regurgatition and aortic stenosis. Tumors of the heart are being operated upon and the patient is often cured. The acute or chronic forms of pericarditis are cured by surgery.

Among the acquired forms of heart disease, syphilitic heart disease, which constituted 13 per cent of our cardiac patients, has disappeared. It has become so rare that many of our hospital interns and residents graduate without ever seeing a patient with syphilis or syphilitic heart disease.

Rheumatic fever, the great scourge of children and young people, has through the therapeutic and prophylatic use of antibiotics and chemotherapeutic agents been controlled to such an extent that in our own locality there has been a reduction of about 85 per cent in the incidence of rheumatic fever. As a result, there are fewer instances of chronic valvular heart disease. Subacute bacterial endocarditis and endarteritis were rarely, if ever, cured, but today a cure is possible because of early diagnosis and the use of anti-bacterial agents.

The degenerative cardiovascular diseases are still one of our great problems. Progress is being made and today we find certain types of hypertension curable by surgery, and many other forms of hypertension can be palliated and the patient's life prolonged comfortably by medical treatment. We have a better understanding concerning arteriosclerosis, and, here again, the surgeon, as noted in a previous paragraph, has brought about both curative and palliative procedures for these individuals. The combined talents of the physician, the surgeon, the neurosurgeon, the roentgenologist, the physiatrist, and the physiotherapist have brought great hope to the victims of cerebral accidents. Many of these vascular accidents can today be treated surgically. Cure and palliation are very common. The collective research of many sub-specialties concerning coronary sclerosis and its complications has led to a return of many of the victims of this disease to a normal community, social and economic life.

The development of our newer drugs such as the anti-coagulants and the diuretics has made it much easier for the victim of heart disease

to return to a compensated or nearly compensated condition so that he can lead a normal or nearly normal life. Better understanding of the altered physiology in cardiovascular disease and in heart failure has brought about better treatment for the victims of heart disease. A better understanding of electrolytes, nutrition and dietary phenomena has added further strength to our armamentarium against heart disease and heart failure.

We recognize that there are many extra-cardiac conditions that influence or express themselves through the cardiovascular system, and we are also aware that certain forms of heart disease are reversible. These are the forms of heart disease which we find are caused by or associated with etiologic factors that are curable. These conditions we see in the congenital forms of heart disease, the problems associated with nutrition, heart disease associated with endocrine disturbances, with infections, injuries to the heart directly or indirectly, and the like.

Time does not permit the inclusion of all of our gains in this war against heart disease. Suffice to say that the examples mentioned illustrate and demonstrate that we have progressed in our war against cardiovascular disease and that the future holds great optimism for the patient suffering from a cardiovascular defect. This new concept of team work in the solution of our problems has been well exemplified by the conquering of many cardiac problems. Optimism in the future is predicated on the past. During the last few years, we have essentially conquered congenital heart disease. The few remaining problems in this field, I am sure, will be solved in the near future. The child born today with a congenital heart defect will, through our present knowledge, be cured and will return to a normal life. The victims of many forms of arteriosclerotic heart disease will be cured by surgical procedures now available and certainly this type of heart disease will soon be preventable as the result of research work being done today. This holds true for all the other forms of degenerative heart disease. We now know that these really are not degenerative phenomena, they are not aging phenomena, they are not physiological phenomena, but they are pathological disturbances, and when their cause is determined the cure will come.

I see, in the near future, the complete control of rheumatic fever as we at this time have complete control of syphilitic heart disease. With the control of syphilitic heart disease, rheumatic fever and congenital heart defects subacute bacterial endocarditis will also disappear and become an esoteric phenomenon.

The victim of congestive heart failure because of the basic research and the unity of many talents and disciplines has found great comfort, and, in many instances, he has been rehabilitated and returned to a normal or nearly normal life.

In his quiet and dedicated manner and his constant support of both basic and clinical research, Louis Mark led many of us 15 years ago to see and accept the *unity of talents;* and hence today we carry on firm in our hope for the complete control and eradication of heart disease.

Clinical Pharmacology of Diuretic Agents with Special Reference to Chlorothiazide (Diuril*)**

RALPH V. FORD, M. D.
Houston, Texas

The factors responsible for congestive heart failure as a clinical syndrome may be multiple. Although decreased cardiac output relative to inflow produces a moderate increase in venous pressure, there is a concomitant decrease in renal blood flow which may contribute to a decreased renal excretion of sodium. There is also a decrease in hepatic inactivation (? due to congestion) of adrenal cortical sodium-retaining hormone. Sodium retention produces at least a transient hypertonicity of the blood which may stimulate hypothalamic osmo-receptors, resulting in increased antidiuretic hormone secretion. Subsequent water retention produces a marked increase in venous pressure to further the development of edema. Thus, the rational therapeutic approach to the problem of congestive heart failure includes the exhibition of agents to increase cardiac output and increase renal blood flow, decrease venous pressure, decrease hepatic failure to inactivate steroids, decrease antidiuretic hormone activity, and decrease the abnormal renal retention of sodium. However, it is the renal retention of (or failure to excrete) sodium that assumes a major role in the pathogenesis of edema and it is this factor that concerns us therapeutically as we discuss diuretic agents. The purpose of this report is to describe the clinical pharmacology of diuretics with special attention to chlorothiazide (Diuril*).

Materials and Methods

A. Pharmacologic Investigations of Chlorothiazide. Ten men between the ages of 41 and 67 with controlled congestive heart failure were the subjects of a previous pilot study.[1] They were maintained on a metabolic ward and were fed a diet containing 50 mEq. of sodium and given 3000 ml. of distilled water to drink daily. This study showed that the effective dose of chlorothiazide lay between 1000 and 2000 mg. In the control state and during the administration of the dosages determined by the pilot study, observations were made of the urinary excretion products in six periods per 24 hours — three consecutive two-hour periods and three consecutive six-hour periods. These included the excretion rates of sodium, potassium, ammonia, chloride, bicarbonate, titratable acidity, total solute, phosphorus, pH, and water.

Ten observations on the 24 hour excretion rate of sodium were made at each dose (1000 and 2000 mg.) and the data (increase in sodium excretion on the day of the drug over the control day) subjected to an analysis of variance. This analysis compares the dosage response curve of chlorothiazide with that of a standard diuretic, meralluride (Mercuhydrin), according to techniques previously described.[2] These data can then be used to determine the "potency estimation" of chlorothiazide compared to meralluride (Mercuhydrin) as well as other diuretics.

*Supplied by Merck Sharp & Dohme Research Laboratories, West Point, Pa.
**From the Departments of Medicine and Pharmacology, Baylor University College of Medicine.

To determine whether renal tolerance to chlorothiazide occurred, an edematous person who had been eating a low sodium (35 mEq.) diet for several years was given 500 mg. of the drug twice daily and the daily weight loss observed over a 15 day period.

One patient was given the drug at a dose of 1000 mg. at 6 A. M. and 6 P. M. on one day to compare the increase in sodium excretion obtained after giving the drug twice daily with that obtained after a single dose.

Another patient was given a dose of 2000 mg. intravenously over a 60-minute period and the increase in sodium excretion compared with that obtained after the same dose was given orally.

B. Clinical Therapeutics. Observations over a period of 18 months for chronic toxicity and beneficial results have been made on 200 patients. Their dosages of chlorothiazide varied from 500 to 2000 mg. daily. Some of these patients were receiving antihypertensive agents in conjunction with chlorothiazide.

C. Comparison of Chlorothiazide with Other Diuretics. Rerefence has been made in this paper to other publications[3] in order to present a comparison of chlorothiazide with other diuretics.

Results

A. Pharmacologic Investigations of Chlorothiazide.

1: Electrolyte Excretion Effects. The data presented graphically in Figure 1 indicate the excretion rates for various observed moieties fol-

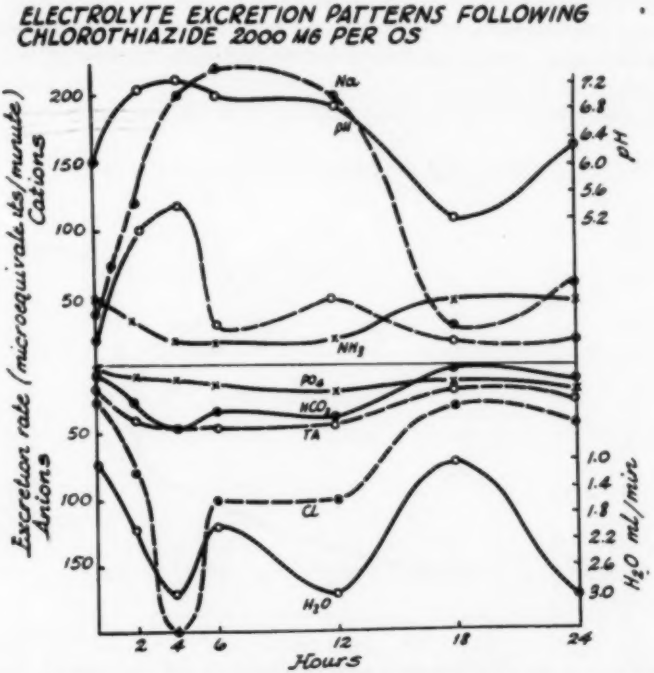

FIGURE 1: Urinary electrolyte excretion patterns (average values 10 patients) following 2000 mg. of chlorothiazide given orally. (Ford, et al, *Arch. of Int. Med.* 100:582, 1957.)

lowing the oral administration of chlorothiazide 2000 mg.[1] The greatest responses were seen during the second two-hour period following the oral administration of the drug, with persistence of the response at a lower level for at least 12 hours and return to control levels during the third six-hour period (18 hours after the drug). The response was characterized by an increase in all moieties observed with the exception of ammonia, which showed a compensatory decrease during the period of drug response and a slight increase at the end of the 24-hour period. Quantitative differences in responses proportional to the dose were observed, but there were no significant qualitative differences in the electrolyte relationships. The greatest responses in excretion rates were observed in sodium and chloride. The magnitude of the increase in potassium excretion was about one-third (or less) that of sodium (and chloride). Ammonia excretion was depressed. Bicarbonate excretion increased from one-tenth to one-fourth that of the chloride excretion. The peak excretion rate was observed at the second 2-hour period, but the total excretion of bicarbonate over a 24-hour period was small. Phosphate excretion was not altered significantly. The pH of the urine increased significantly immediately and began to fall four hours after the drug was administered.

2. Dose-Response Relationships. The pilot study indicated that the effective dose lay between 1000 and 2000 mg.; hence repeated observations were made at these two doses.[1] A dose of 4000 mg. produced no toxic effects but demonstrated no additional diuretic effectiveness (Fig. 2). Since the subjects of the bioassay were given a constant diet containing 50 mEq. of sodium, the control excretion in the urine was approximately 90 per cent of the dietary sodium (about 45 mEq.). The average increase in the 24-hour urinary sodium was 44 mEq. after the

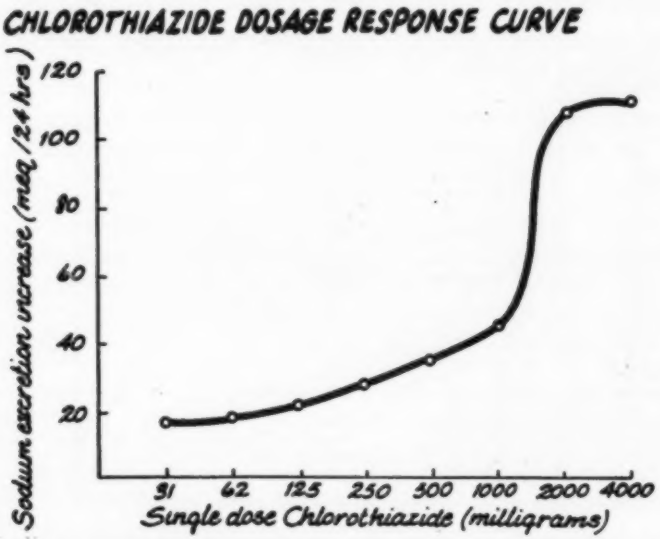

FIGURE 2: Chlorothiazide dose response curve. (Ford, et al, *Arch. of Int. Med.* 100: 582, 1952.)

1000 mg. dose and 104 mEq. after the 2000 mg. dose (Fig. 3). When these increases are compared to those following the administration of a standard parenteral mercurial diuretic agent meralluride (Mercuhydrin) by an analysis of variance, the dose response curves are found to be highly significant and parallel (P 0.001), so that a calculation of "potency estimation" can be made.[1,2]

3. Comparative Potency of Chlorothiazide. When potency of chlorothiazide is compared with other diuretics (1), it appears that a dose of 40 mg. of mercury equivalent of diglucomethoxane (Mersoben) (1 cc., I.M.) produces an increase in sodium excretion that is equivalent to 1562 mg. of chlorothiazide administered orally, or 1 cc. of intramuscular meralluride (Mercuhydrin) is equivalent to 1119 mg. of oral chlorothiazide and 1 cc. of mercaptomerin (Thiomerin) administered parenterally is equivalent to 671 mg. of oral chlorothiazide. Four tablets (40 mg. mercury equivalent) of chlormerodrin (Neohydrin) administered orally are equivalent in natriuretic potency to 560 mg. of chlorothiazide.

4. Repetitive Effectiveness of Therapy. The persistence of diuresis as manifest by weight loss accompanying the continuous twice daily administration of chlorothiazide is well demonstrated (Fig. 4). This feature has further substantiating evidence in the group of chronically treated outpatients described below.

5. Effectiveness of Fractional Dosages of Chlorothiazide. In a patient who received the drug at a dose of 1000 mg. twice within a 24-hour period, the excretion pattern for sodium was repeated after the second dose in a fashion similar to that following the first dose but at a higher level, and the total increase in sodium excretion per 24 hours was greater

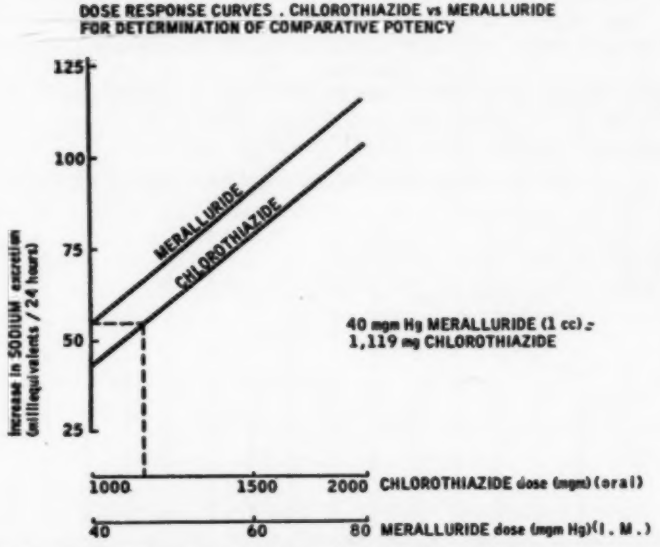

FIGURE 3: Dose-response curves for chlorothiazide (Diuril) versus meralluride (Mercuhydrin) for determination of comparative potency. The increase in sodium excretion plotted against the dose (in logarithmic order) for a standard diuretic (Mercuhydrin) intramuscularly administered and chlorothiazide orally administered permits a direct reading of potency (dotted line).

than after a single dose of 2000 mg., indicating the advantages of fractional doses. There was no increase in the degree of natriuresis associated with four fractional cases.

6. Oral vs. Intravenous Administration of Chlorothiazide. Comparison of the enhanced sodium excretion in one patient following intravenous and oral administration of chlorothiazide 2000 mg., indicates that the latter is the more effective method for clinical use (Fig. 5). This is compatible with data showing that the drug is almost totally excreted within six hours following intravenous administration, whereas with the oral dose, one-half is excreted in 24 hours and excretion is completed in 48 hours.[4]

B. Clinical Therapeutics.

1. Recommended Dosage Schedule. From personal experience in over 200 patients treated over a period of 18 months, I believe it best to administer two doses daily — one after breakfast and one after lunch. This is to avoid or decrease nocturnal diuresis. If the degree of edema is not dangerous, a daily dose of 500 mg. only after lunch might be started and increased slowly over a three to 10 day period to 500 mg. after breakfast and lunch, then to 1000 mg. after breakfast and lunch if necessary. A small group of patients may be sensitive to drastic diuresis and complain bitterly of weakness if the large doses are used initially. It must be remembered, also, that the hypertensive patient receiving, concurrently, a ganglionic blocking agent will experience a greater degree of orthostatic hypotension when this diuretic agent is added to the therapeutic regimen.

The prolonged outpatient use of chlorothiazide in congestive heart failure has fallen roughly, into three categories. One-fourth of the patients have been stabilized and maintained edema-free with 500 mg.

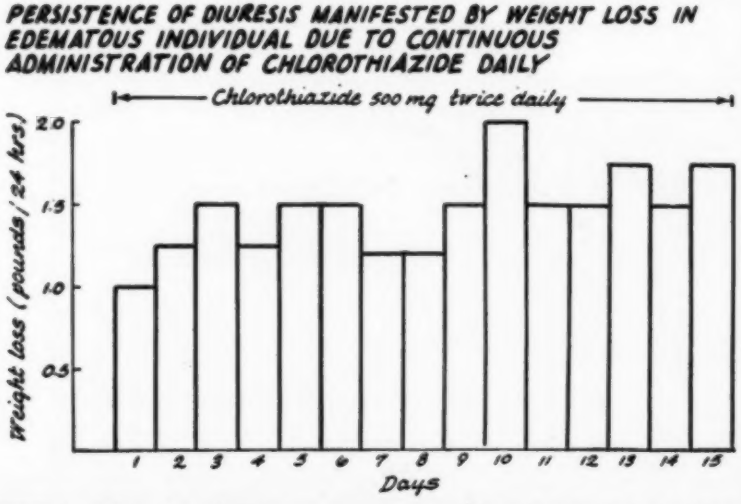
PERSISTENCE OF DIURESIS MANIFESTED BY WEIGHT LOSS IN EDEMATOUS INDIVIDUAL DUE TO CONTINUOUS ADMINISTRATION OF CHLOROTHIAZIDE DAILY
Chlorothiazide 500 mg twice daily
Weight loss (pounds/24 hrs)
2.0
1.5
1.0
0.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days

FIGURE 4: When the edematous person is given chlorothiazide daily for long periods of time, there is no loss of diuretic effectiveness as manifested by weight loss. (Ford, et al, *Arch. of Int. Med.* 100:582, 1957.)

daily. One-half have required 500 mg. twice daily. The other one-fourth have required 1000 mg. twice daily. This daily therapeutic regimen has been followed by over 200 patients for more than one year without evidence of serious toxicity specifically attributable to chlorothiazide.

2. Chronic Toxicity. The long-term (18 months) use of this drug in over 200 patients has been remarkably free of serious toxic reactions. Four electrolyte imbalance states have been classified: (1) chronic dilutional hyponatremia, (2) hypochloremic alkalosis, (3) "salt depletion" syndrome, and (4) potassium deficiency.[5] Complaints of weakness have been observed in 20 per cent of the patients receiving large doses of chlorothiazide as opposed to 25 per cent in patients receiving 2 cc. of meralluride (Mercuhydrin) intramuscularly. It is only in hospitalized patients on strict sodium restriction that we have observed hypochloremic alkalosis (treatment discussed below) and only in the very far advanced problem of myocardial degeneration have we observed dilutional hyponatremia. It is to be noted that these reactions are not peculiar to chlorothiazide but may be observed with mercurial diuretics as well. Clinically significant hypokalemia has been observed in only one patient, a 45 year old man with cirrhosis and ascites. He did not experience diuresis with chlorothiazide but continued to receive the drug inadvertently for a seven-day period. It is quite true that patients receiving chlorothiazide daily for extended periods of time will demonstrate a 15 to 30 per cent reduction in the serum potassium level but these patients do not present a truly significant clinical syndrome of hypokalemia.

Another complication of diuretic therapy is potassium deficiency. This may precipitate digitalis toxicity. Clinically, extreme muscle weakness, cardiac irregularities and abdominal distention are clues that should lead to the diagnosis. Ingestion of 6 to 8 ounces of orange juice on the day of diuretic therapy is usually adequate insurance against this complication. Should the complication occur, oral potassium chloride in dosages of 2 to 5 grams daily is indicated.

Ultimately, failure to respond to diuretics will be due to progressive impairment of glomerular filtration (secondary to decreased cardiac output) to such a degree that little sodium is filtered. Then virtually all of the sodium is reabsorbed, even after maximal tubular depression with diuretics. However, failure of diuresis may ensue because of an electrolyte imbalance which disrupts the normal biochemical architecture. This is usually a complication of too vigorous diuretic measures and too rigid salt restriction or progressive myocardial degeneration.

Chronic dilutional hyponatremia is one of the most serious metabolic derangements and is apparently unrelated to treatment unless concurrent primary renal disease is present. Under the latter circumstances, if fluids of low sodium content are given in excess of the kidney's ability to excrete water, dilutional hyponatremia results. The syndrome results from extreme dilution of extracellular fluid. Presumably excessive antidiuretic hormone activity may also cause this syndrome. In the absence of severe primary renal disease in patients with heart failure, the syndrome is indicative of severe myocardial impairment. Serum sodium and serum chloride are low although total body sodium is excessive.

Hypochloremic alkalosis and "salt depletion" syndrome occur as a complication of vigorous therapy with saluretic agents and rigid dietary salt restriction. In hypochloremic alkalosis, the main deficit is chloride. In "salt depletion" syndrome, it is sodium. Clinically, there are lassitude, apathy, anorexia, oliguria and diuretic fastness in both. Hypochloremic alkalosis is also usually indicative of severe myocardial disease. It is difficult to produce this syndrome in normal subjects or in patients with only mild heart failure, even with vigorous daily diuretic administration. Therapy of hypochloremic alkalosis is directed at replacement of the appropriate electrolyte, using oral ammonium chloride. For this purpose at least 2 grams (30 grains) should be given every four hours. It is best to give the drug after a meal in order to avoid nausea and vomiting. Hypochloremic alkalosis can easily be avoided if ammonium chloride is given to predisposed individuals concurrently with the administration of diuretics that produce chloruresis.

The sodium deficit in patients with hyponatremia may be calculated from the serum sodium values, and replacement can be based on such calculations. Calculations may be based on extracellular (including intravascular) fluid sodium concentrations using 5% sodium chloride for replacement purposes. Thus 20 per cent of body weight (kilograms) is the approximate volume of the extracellular fluid. The plasma sodium

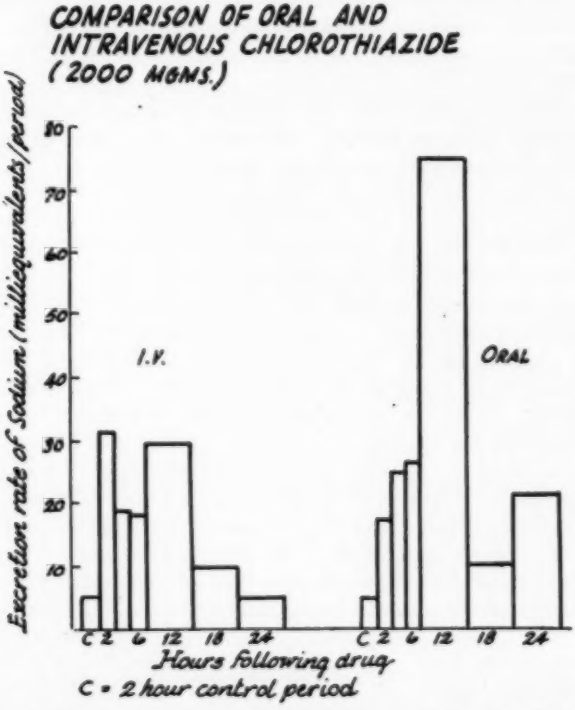

FIGURE 5: Although intravenous administration of chlorothiazide is associated with a slightly more rapid onset of increased sodium excretion, the total excretion is less than that following oral administration (2000 mg.). (Ford, et al, *Arch. of Int. Med.* 100:582, 1957.)

concentration is about the same as the extravascular, extracellular fluid sodium concentration. Therefore, normal plasma sodium (140 mEq.L.) minus the measured plasma sodium (milliequivalents) to correct the hyponatremia in the extracellular fluid compartment. One milliequivalent of sodium chloride equals 0.85 cc. of 5 per cent salt. Thus:

$$\frac{\text{Body Wt. (Kgms.) X .20 X (140—patients plasma sodium in mEq.)}}{.85}$$

—cc. of 5 per cent sodium chloride to be administed.

This salt should be given slowly by intravenous infusion over a period of two hours or more. It is important to restrict fluids (especially water) while the 5 per cent salt is being given and for some time thereafter. Otherwise the plasma sodium will be diluted again, the blood volume increased and the heart failure aggravated. After 12 hours, thus allowing adequate time for equilibrium and stability to occur, the plasma sodium concentration should again be determined. The process must then be repeated if hyponatremia continues. It is an error in our opinion to attempt to bring sodium levels entirely to normal. Furthermore, only if the sodium level is below 125 mEq. is corrective therapy with 5 per cent salt indicated and then only if the clinical symptoms demand it (severe oliguria, extreme weakness and lethargy, and cerebral symptoms). Otherwise, a liberalized salt intake will suffice. After the syndrome is corrected, the patient is then treated as a severe cardiac employing bed rest, digitalis and diuretics as before.

In summary, most of the complications of diuretic therapy may be avoided by (1) observation of the patient, (2) the use of these drugs only when indicated, and (3) full realization of their pharmacologic attributes.

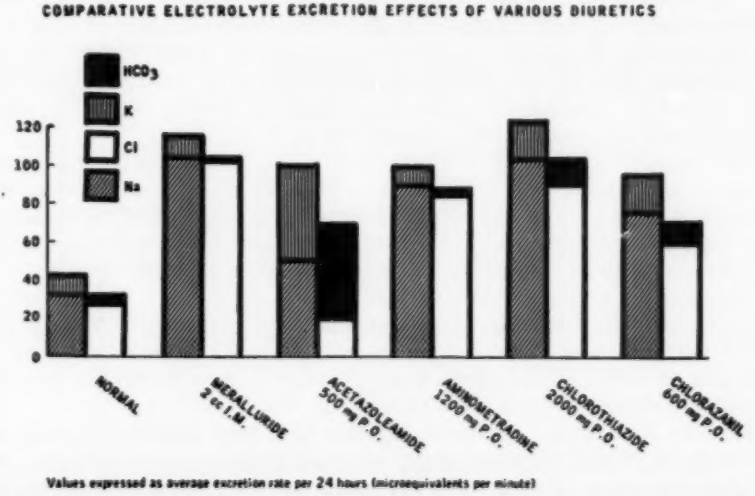

FIGURE 6: The electrolyte excretion patterns of five diuretic groups may be differentiated on the basis of the effects on sodium, potassium, chloride, and bicarbonate. Although other ions are influenced in varying degrees by the five different diuretics, the greatest change which is common to all is observed in sodium excretion.

C. *Comparison of Chlorothiazide with Other Diuretics.*

1. Pharmacodynamics of Five Classes of Diuretics. Chlorothiazide differs from other diuretic agents both in its chemical structure and its pharmacodynamic effect on the excretion of various electrolytes (Fig. 6).[5]

The urinary electrolyte excretion pattern following the intramuscular administration of meralluride (Mercuhydrin) is typical of the patterns produced by the other mercurial diuretics. The onset of drug action occurs within two hours and lasts for 12 to 18 hours. There is a predominant augmentation of sodium and chloride excretion (Fig. 6) without significant alteration in potassium excretion. During the period of greatest sodium loss (two to six hours), ammonia excretion is slightly depressed. Bicarbonate excretion is suppressed during the period of greatest chloruretic response, but rises to normal or above normal when this period is over. Phosphate excretion is similar to that of bicarbonate. Continuous daily therapy is repetitively effective in the absence of biochemical dysequilibrium.

The oral administration of acetazoleamide (Diamox) produces a urinary electrolyte excretion pattern typical of the carbonic anhydrase inhibitors (Fig. 6). The predominant effect is the augmentation of the excretion of sodium with an almost equal effect on potassium and bicarbonate excretion. The onset of drug action occurs within six hours, and persists for six to 12 hours. During the period of greatest bicarbonate loss, chloride excretion is suppressed, but increases as the rate of bicarbonate excretion. The onset of drug action occurs within six hours, and significantly altered. Drug "tolerance" appearing on the second day of continuous therapy prevents repetitive effectiveness and demands an interrupted dosage schedule.

Aminometradine (Mictine) and its isomer aminoisometradine (Rolicton) produce an increased sodium and chloride excretion (Fig. 6). These aminouracils act within two to four hours; their duration of action is approximately 12 hours. There is no significant effect on potassium, bicarbonate, ammonia or phosphate excretion. Drug "tolerance" appearing on the second day of continuous therapy prevents repetitive effectiveness and demands an interrupted dosage schedule.

Oral administration of chlorothiazide (Diuril) causes a significant increase in sodium and chloride excretion which appears within two hours and lasts for approximately 12 hours (Fig. 6). Potassium excretion increases about one-third as much as sodium. Ammonia excretion is not altered (or slightly depressed) during the period of natriuresis, but increases during the ensuing 12 hours. This is probably a compensatory renal mechanism to conserve sodium. The excretion of phosphate is not significantly altered. Bicarbonate excretion is about one-fourth that of chloride excretion. Continuous daily therapy is repetitively effective in the absence of biochemical dysequilibrium.

Another chemically different diuretic is a new triazine compound. Chlorazanil (Daquin), when orally administered, augments sodium and chloride excretion (Fig. 6). The excretion rate of potassium is increased to about one-third that of sodium excretion. Ammonia excretion is suppressed during the period of greatest natriuresis, but increases in the following twelve hour period. The concentration of solutes is less than that

seen with comparably potent natriuretic agents suggesting that there is possibly a primary effect on water excretion. There is no significant alteration in phosphate excretion. Bicarbonate excretion is increased to about one-fourth that of chloride. Continuous daily therapy is repetitively effective unless there is biochemical imbalance.

These five classes of diuretics present differing electrolyte excretion patterns suggesting that their mechanisms of action are different although the principle action of each is the augmentation of the urinary excretion of sodium. This information may be of clinical importance in the intelligent selection of a diuretic to satisfy particular therapeutic needs in congestive heart failure with varied complicating situations. More precisely, these electrolyte excretion effects may be correlated with changes in the biochemical architecture occurring following the continuous administration of the diuretic agents. Thus, one may predict that the continuous loss of sodium and chloride will be associated with a tendency to the development of hypochloremic alkalosis and the low salt syndrome (mercurials and chlorothiazide). The continuous loss of bicarbonate (especially in the patient with poor or borderline renal compensation) may lead to a significant metabolic acidosis (with carbonic anhy-

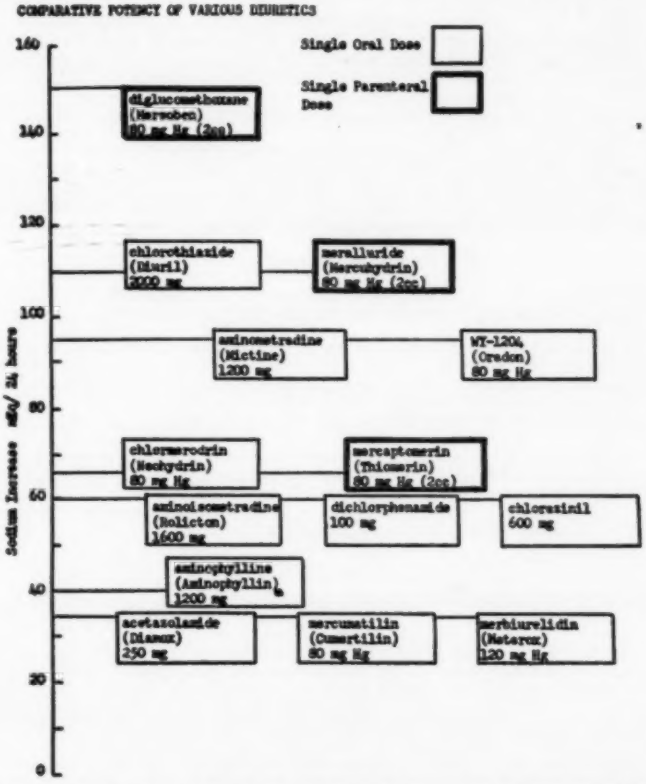

FIGURE 7: This chart provides a comparison in terms of sodium excretion of the relative potency of various diuretics at the maximum clinically tolerated dosages of each. (Ford, R. V., *Ann. of the N. Y. Acad. of Sci.* 71:397, 1958.)

drase inhibitors). The continuous loss of potassium (chlorothiazide and carbonic anhydrase inhibitors) may aggravate a pre-existent hypokalemia, e.g. cirrhotics, etc.

2. Comparative Potency of Various Diuretics. Figure 7 shows the relative potency of various diuretic agents by comparing the increase in sodium excretion produced after administration of the maximum single dose which is tolerated clinically in over 75 per cent of the patients. That is, this dose is toxic (usually gastrointestinal) in less than 25 per cent of the patients tested. Thus, chlorothiazide is equipotent to meralluride and more potent than chlormerodin, aminometradine, acetazoleamide, and chlorazanil.

To summarize the clinical application of diuretic therapy on the basis of drug tolerance, biochemical changes associated with continuous use, and finally potency, two groups of agents seem to be superior—mercurials and chlorothiazide. Since convenience of administration and economy must frequently be considered in the selection of a diuretic agent and since the oral administration of chlorothiazide is roughly equipotent with meralluride intramuscularly, chlorothiazide appears to be the current drug of choice.

SUMMARY

1. The clinical syndrome of congestive heart failure may be logically and effectively treated with diuretics although their use is not directed at the primary derangement.
2. Chlorothiazide therapy in congestive heart failure produces a significant loss of sodium and chloride via the kidney in almost physiologic proportions. It is effective orally in initiating therapy for edema and the maintenance of the edema-free state. The dose varies from 500 mg. to 2000 mg. daily. Adverse side reactions are minimal and not peculiar to this drug but are shared with any potent diuretic.
3. Comparison of chlorothiazide with mercurials, aminouracils, carbonic anhydrase inhibitors, and a triazine diuretic on the basis of potency, repetitive effectiveness, disturbances in biochemical architecture, and economy, indicates that chlorothazide is the current diuretic of choice in congestive heart failure.

RESUMEN

1. El síndrome clínico de insuficiencia cardiaca congestiva puede ser tratado lógicamente y efectivamente por los diuréticos aunque su uso no se dirige hacia la afección primordial.
2. El tratamiento con la clorotiacida en la insuficiciencia cardiaca congestiva produce una pérdida de sodio significante así como de cloro por la vía renal casi en proporciones fisiológicas. Es efectiva oralmente al iniciar el tratamiento de edema, así como para mantener un estado libre de edema. La dosis varía de 500 a 2,000 mg. diarios. Las reacciones adversas son mínimas y no son peculiares a la droga, sino las que son de esperarse en un diurético potente.
3. La comparación de la acción de la clorotiacida con los mercuriales, los aminouraciles, los inhibidores de la anhidrasa carbónica y la triacina, como diuréticos sobre de la base de potencia, efectividad en la reiteración de su uso, trastornos de la arquitectura bioquímica y economía indica que la clorotiacida es el diurético actual de elección en la insuficiencia cardiaca congestiva.

RESUMÉ

1. Le syndrome clinique de défaillance cardique peut être logiquement et efficacement traité par des diurétiques, bien que leur emploi ne soit pas dirigé contre l'altération première.
2. Le traitement par la chlorothiazide dans la défaillance cardiaque produit une perte marquée de sodium et de chlore par le rein presque dans les proportions physiologiques. Il est efficace par la bouche pour entreprendre le traitement de l'oedème et pour évitar son apparition. La dose varie entre 500 mmg. et 2.000 mmg. quotidiennement. Les réactions toxiques sont minimes et non pas particuliéres à ce produit mais telles qu'elles existent lorsqu'on utilise tout diurétique actif.
3. La comparaison de la chlorothiazide avec les diurétiques mercuriels, les aminouraciles, les inhibiteurs à base d'anhydride carbonique et un diurétique triazine indique que, sur le plan de la puissance d'action, de l'efficacité en cas d'utilisation itérative, des modifications de l'architecture biochimique et de l'économie, la chlorothiazide est le diurétique courant électif dans la défaillance cardiaque.

ZUSAMMENFASSUNG

1. Das klinische Syndrom der Herzinsuffizienz mit Stauung kann folgerichtig und wirksam mit Diuretizis behandelt werden, obwohl deren Bebrausch nicht gegen die primäre Störung gerichtet ist.

2. Chlorothiazid-Therapie bei Herzinsuffizienz mit Stauung bewirkt enie beträchtliche Ausscheidung von Natrium und Chlor durch die Niere unter fast physiologischen Verhältnissen. Sie ist oral wirksam als einleitende Ödembehandlung und zur Aufrechterhaltung des ödemfreien Zustandes. Die Dosis schwankt zwischen 500 und 2000 mmg täglich. Ungünstige Nebenwirkungen kommen selten vor und sind nicht diesem Mittel eigentümlich, sondern mit jedem wirksamen Diureticum verknüpft.

3. Ein Vergleich von Chlorothiazid mit Quecksilberpräparaten, Aminourazil, Kohlensäureanhydrase-Hemmstoffen und einem Triazin-Diureticum auf der Basis der Stärke, Kirksamkeit bei Wiederholungen, Störungen des biochemischen Gleichgewichtes und der Wirtschaftlichkeit ergibt, daβ das Chlorothiazid z.Zt. das Diureticum der Wahl bei mit Stauung verbundener Herzinsuffizienz darstellt.

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Myocardial Infarction in Young Adults*

THOMAS N. JAMES, M.D., F.C.C.P.,[1,**] and ROBERT W. BROWN, M.D.[2]
New Orleans, Louisiana

The infrequency of myocardial infarction in young adults has been of considerable investigative interest. Although most studies have been of small groups,[1-8] some have assumed encyclopedic proportion.[9,10] Because of difficulty in obtaining large series of cases, two augmenting approaches have been previously employed. One of these was to utilize the age of 40 years as the upper limit, a choice deliberately determined for the purpose of obtaining a large number of patients to study.[9,11] The other approach was to employ retrospective analysis of cases diagnosed in the military services, where large numbers of young men are available; this type of study utilized case material from necropsies[10,12,13] and also from indexed diagnoses in both surviving and fatal cases.[10,14]

That both of these approaches have provided an immense amount of valuable information is unquestionable. However, as more is learned about myocardial infarction, it is becoming apparent that the incidence of this disease in patients in their late 30's becomes so high that results of analysis of these cases may differ little, if any, from those of older patients. As examples of this upswing, the 100 patients younger than 40 years of age studied by Glendy, Levine and White[11] included eight ages 20 to 29, 17 ages 30 to 34, and 75 ages 35 to 39; in the study by Master, Dack and Jaffe[15] of 500 cases of myocardial infarction one was 27, five were 30 to 34, and 33 were 35 to 39.

Regarding the second augmenting approach, problems are readily apparent in evaluating information obtained by studying young men in military service, a situation involving a pre-selected population. For example, the incidences of diabetes and hypertension are artificially low compared with the general population, since these diseases are a basis for exclusion from the services. Additionally, there is evidence that the muscular, robust young man is ironically the one for whom myocardial infarction has predilection;[9] this, of course, is the typical candidate for military service, so one might postulate that the services choose the type of person in whom myocardial infarction is most likely to develop.

To examine these questions further this study was undertaken to compare facts about myocardial infarction as observed in private patients and in armed forces veterans. It consisted of patients aged 35 years and younger, admitted to the Veterans Administration Hospital in New Orleans and Ochsner Foundation Hospital since 1945. The diagnoses were examined for acceptability on the basis of clinical information (history, physical findings, laboratory and electrocardiographic evidence) or observations at necropsy. During this period of more than 12 years there were 43 acceptable cases, 16 at the private hospital and 27 at the veterans' hospital. During the same period of time among 53,443 admis-

*From the Section of Cardiology, Ochsner Foundation Hospital[1] and the Veterans Administration Hospital (Tulane Service).[2]
**Present address: Henry Ford Hospital, Detroit, Michigan.
Dr. Brown was a U. S. Public Health Service Fellow, Department of Medicine, Tulane University School of Medicine. Present address: Fort Worth, Texas.

sions to the veterans' hospital myocardial infarction was diagnosed (including all age groups) 1174 times; at the private hospital among 70,267 admissions myocardial infarction was diagnosed 1669 times.

Results

The distribution of patients when the myocardial infarction occurred, according to age, sex and hospital, is shown in Table 1. What the patients were doing at the time of the attack is presented in Table 2. Five of the 11 private patients but only two of the 12 veterans in whom this information was available were asleep when the infarction began. The onset of infarction occurred during mild exertion in four of the 11 private patients and in five of the 12 veterans.

In Table 3 the duration of pilot angina is recorded. Nine of the 26 veterans in whom this information was available had no previous symptoms, whereas only 3 of the 16 private patients had no prior pain. One of the latter 3 patients had chronic ulcerative colitis and it is difficult to be certain some of the gastrointestinal pain did not mask angina or vice versa. Six of the 16 private patients and six of the 26 veterans had had pain for more than 12 months.

The distribution of cases according to associated pertinent diseases is shown in Table 4. Seven of 16 private patients had diabetes, hypertension or hypercholesterolemia; six of 27 veterans had one of the three.

TABLE 1 — DISTRIBUTION OF 43 CASES OF MYOCARDIAL INFARCTION ACCORDING TO AGE, SEX AND HOSPITAL

Age (years)		26	27	28	29	30	31	32	33	34	35	Total
O. F. H.* —	Men	1	0	1	1	2	2	1	2	0	2	12
	Women	0	0	1	0	0	1	0	1	1	0	4
V. A. H.**		1	0	1	5	3	2	4	2	3	6	27

*Ochsner Foundation Hospital
**Veterans' Administration Hospital, New Orleans

TABLE 2 — ACTIVITY AT ONSET OF MYOCARDIAL INFARCTION IN 43 YOUNG ADULTS

Age Group	26 — 30 years		31 — 35 years	
Hospital	OFH	VAH	OFH	VAH
Asleep	3	1	2	1
Awake (resting)	0	1	1	2
Mild exertion	2	1	2	4
Strenuous exertion	0	0	1	2
Unknown	1	7	4	8
Totals	6	10	10	17

TABLE 3 — INTERVAL BETWEEN FIRST SYMPTOM AND INFARCTION IN 43 YOUNG ADULTS

Age Group	26 — 30 years		31 — 35 years	
Hospital	OFH	VAH	OFH	VAH
Less than 1 month	2	2	1	2
1 — 6 mo.	0	2	2	2
6 — 12 mo.	0	2	2	1
Over 12 mo.	2	1	4	5
None	2	3	1	6
Not stated	0	0	0	1
Totals	6	10	10	17

TABLE 4 — DISEASES RELATED TO MYOCARDIAL INFARCTION IN 43 YOUNG ADULTS

Age Group	26 — 30 years		31 — 35 years	
Hospital	OFH	VAH	OFH	VAH
Diabetes	2	0	0	0
Hypertension	0	0	3	5
Hypercholesterolemia	0	0	2	1
Atherosclerosis only	4	10	5	11
Totals	6	10	10	17

TABLE 5 — FAMILY HISTORIES PERTINENT TO MYOCARDIAL INFARCTION IN 43 YOUNG ADULTS (DIABETES, HYPERTENSION, CEREBRAL OR CORONARY ATHEROSCLEROSIS)

Age Group	26 — 30 years		31 — 35 years	
Hospital	OFH	VAH	OFH	VAH
Father	3	1	0	3
Mother	0	0	0	4
Both Parents	0	4	2	2
Sibling	1*	0	0	2
Grandparents	0	0	3	0
Negative history	2	4	5	5
Unknown	1	1	0	1
Totals	7 (One listed twice)	10	10	17

*Also had father with positive history

In nine of the 16 private patients the myocardial infarction was due to atherosclerosis with no pertinent associated disease, whereas in 21 of the 27 veterans it was on this basis. None of the patients in either group had both diabetes and hypertension. None of the veterans was diabetic.

The relation of family history to myocardial infarction in the two groups is shown in Table 5. In five of the 15 private patients with recorded family histories one or both parents had diabetes, hypertension or atherosclerotic cardiovascular disease; of the other 10, three had grandparents with diabetes, and one had an uncle who was diabetic. In 25 veterans with family histories available (one of the two without history was adopted) 16 had positive histories of these diseases in one or both parents; two of the remaining nine had a sibling with diabetes.

Body weight in the two series is compared in Table 6. Seven of the 22 veterans whose size was known were underweight; only one of the 16 private patients was. Overweight was recorded in three of 22 veterans and three of 16 private patients. Twelve patients in each group had weights within 15 pounds of average for their height.

Various febrile diseases preceded the acute myocardial infarction in five of the 16 private patients and four of the 27 veterans, being of suffi-

TABLE 6 — WEIGHT OF 43 YOUNG ADULTS WITH MYOCARDIAL INFARCTION

Age Group	26-30 years		31-35 years	
Hospital	OFH	VAH	OFH	VAH
More than 15 lb. overweight	0	1	3	2
More than 15 lb. underweight	1	2	0	5
Within 15 lb. of average	5	6	7	6
Not recorded	0	1	0	4
Totals	6	10	10	17

cient severity to be recorded in the history; similar but less severe illnesses may have preceded the attack in others. Of particular interest were a 31 year old hypertensive woman who had fever and a purulent cough for one week seven days before she died of acute occlusion of the left anterior descending coronary artery (necropsy); a 32 year old veteran who had fever after tonsillectomy 10 days before infarction occurred; a 29 year old veteran who had a sore throat treated with penicillin shots seven days before occurrence of the infarction; and a 34 year old veteran who had daily slight fever of undetermined origin for one month prior to the attack of infarction, which occurred while he was hospitalized for investigation of the cause of the fever.

In both the private patients and the veterans, pericarditis was a prominent differential consideration on admission, but in all the cases accepted for this study the evidence for acute myocardial infarction was conclusive.

Because some patients were lost to follow-up at varying intervals after their attacks, and because the post-infarction period ranged from two months to 12 years, detailed analysis of overall survival rates or specific prognosis is not warranted. Some of the valid follow-up data were as follows. Five of the 16 private patients are dead (2 necropsies); four of the 27 veterans are dead, two of myocardial infarction and two of pulmonary embolism (all necropsies). Eighteen of the 27 veterans made good initial recoveries, while the remaining five survivors were invalided because of angina, congestive failure or cerebrovascular accident. Nine of 16 private patients made good initial recoveries, but two of these subsequently died, one of a pulmonary embolus after sympathectomy, and the other suddenly at home of unknown cause. Six of the 16 private patients were invalided after their initial attack, with angina or congestive heart failure; two of these subsequently died. The fifth death in the private patients was a young hypertensive woman who died within 24 hours after onset of the myocardial infarction.

Discussion

These observations allow the examination of certain questions regarding the validity of two aspects of previous studies on myocardial infarction in young adults. First, should patients older than 35 years be included in such studies; and second, how valid are studies done on selected predominantly male populations (such as young soldiers or veterans) when a disease is considered in relation to all patients?

Regarding the first question, it is interesting that in one study of 100 patients younger than 40 years of age only three were women,[8] whereas in our study of 16 private patients aged 35 years or younger four were women; this is a comparative percentage of 3 and 25. Such a difference would imply that inclusion of patients with a myocardial infarction between the ages of 35 and 40 years may distort the characteristics of infarction in "young" adults; and additionally, that whereas most patients with infarction between the ages of 35 and 40 years are men, this is less true in patients younger than 35 years.

In their study of 500 cases of myocardial infarction Master and associates[15] had 39 patients younger than 40 years of age, of whom 33 were between 35 and 39. They concluded that diabetes, hypertension and a familial or hereditary tendency did not correlate with susceptibility to coronary disease. In our 43 patients younger than 35 years, 13 had diabetes, hypertension or hypercholesterolemia, and 21 of the 43 had positive family histories of these diseases or clinically manifest atherosclerosis. This discrepancy again may be due partly to inclusion of patients between the ages of 35 and 39 years, a much larger percentage of whom has myocardial infarction due to atherosclerosis without pertinent associated diseases.

In contrast to the discrepancies described above, which are introduced by the age group of 36 to 40 years, it is significant that the data presented in our six tables for patients 35 years or younger show no preponderance for younger or older subjects.

In other words, patients aged 35 years and younger may be considered a reasonably homogeneous group in relation to myocardial infarction.

Regarding the question of validity of all-male (or predominantly male) studies, the first reservation which comes to mind is that such studies ignore roughly half the population. This would be less important if myocardial infarction were rarer than it is in young women (conceding it is relatively rare in any young adult), but in our study in the series including both sexes one-fourth were women. It may be added that all four of these young women had diabetes, hypertension or hypercholesterolemia, but for the purpose of this study they all also had myocardial infarction. This lack of myocardial infarction due to "spontaneous" atherosclerosis in women who have not yet undergone the menopause is supported by other reviews on the subject.[15-17]

The role that preceding infections may play in the onset of myocardial infarction is intriguing. Newman[16] suggested that atheroma may be a consequence of infection. In a study of the coronary arteries of infants Minkowski[18] presented a lucid review of the evidence for and against this association, pointing out that there is a formidable array of evidence and workers on either side. In his study of 204 infants, however, he concluded that acute infectious diseases unequivocally play a role in production of thickened intima of the coronary arteries. In view of this, one is impressed by the high incidence of preceding infections in the present series (nine of 43 cases). It suggests that in young patients complaining of pain in the chest who have had a preceding febrile illness one should consider the possibility of myocardial infarction as well as pericarditis or non-cardiac disease.

Two of the most frequently analyzed features in reviews on myocardial infarction are the relationship of onset to exertion, and frequency of obesity. Onset during mild activity was similar in both our groups (three of 16 and six of 27 patients) while onset during strenouous exertion was uncommon in either group (0 of 16 and three of 27). Obesity was uncommon in either of our groups, only six of 42 patients with recorded weights being obese while eight were underweight. Twelve of 43 patients had had no preceding ("pilot") angina before infarction, while 12 others had had intermittent pain for more than 12 months.

In both groups the overall incidence of myocardial infarction (including all ages) was slightly more than 2 per cent of all admissions. The incidence of young adults (aged 35 years or less) was higher in the veterans' group, however, being 2.3 per cent (27 of 1174 infarcts) as compared with 1.0 per cent (16 of 1669) of the private patients with infarction. The reason for the increased vulnerability of young adults in the veterans' group is not clear; it may be related to a larger percentage of robust and muscular young men in the services.

Prognosis for myocardial infarction in young adults depends on so many variables that it is questionable whether general statements should be made. The incidences of associated diabetes and hypertension, for example, are thought to influence survival after infarction. We believe a high incidence of these diseases is probably characteristic of myocardial infarction in patients younger than the age of 35 years. However, there was a striking difference in incidence of these diseases among the fatal cases in our two groups. All four of the veterans who died had myocardial infarction due to atherosclerosis only, whereas in the private patients — who had a higher mortality rate — two of the five patients who died were hypertensive, one was a juvenile diabetic, and only two had atherosclerosis alone.

Three facts summarize an important difference regarding diseases associated with atherosclerosis in the two groups studied. First, all 4 veterans who died had myocardial infarction presumably due to atherosclerosis only, whereas three of five private patients who died had associated diseases believed to have influenced the atherosclerosis. Second, none of the veterans dead or surviving was diabetic. Third, myocardial infarction due to atherosclerosis without pertinent associated disease was more prevalent among the veterans (21 of 27 cases) than among the private patients (nine of 16 cases). We believe these facts make it difficult to equate data from any two such groups.

SUMMARY AND CONCLUSIONS

1. Myocardial infarction occurring in patients 35 years old or younger was compared between 27 patients from a veterans' hospital and 16 patients from a private hospital. The following differences were noted: The infarct was due to atherosclerosis without associated pertinent diseases in a larger percentage of the veterans than private patients, and this was especially true in the fatal cases; a larger segment of the total number of infarcts was composed of young adults at the veterans' hospital than at the private hospital; one-fourth of the series that included both sexes were women.

2. Because reported reviews of myocardial infarction in patients aged 36 to 40 years seem similar to older patients and different from patients 35 years and younger, it is suggested that in future studies on myocardial infarction in "young" adults the maximum age be 35 years.

3. Although much of the data regarding myocardial infarction in young soldiers and veterans is applicable to the disease in the general population, some which is not has been discussed.

RESUMEN Y CONCLUSIONES

1. Se llevó a cabo una comparación entre enfermos de 35 o menos años afectados por infarto del miocardio entre dos grupos: uno de 27 enfermos de un hospital de Veteranos y 16 enfermos de un hospital privado. Se notaron las diferencias siguientes: El infarto fué debido a la ateroesclerosis sin otra enfermedad pertinente asociada en un porcentaje mayor de veteranos que en los enfermos de práctica privada y esto especialmente cierto en los casos fatales; una mayor proporción del número total de infartos correspondía a jóvenes adultos en el hospital de veteranos que en el hospital privado; un cuarto de las series que incluyeron ambos sexos fué de mujeres.

2. En vista de que se ha relatado que no hay diferencia entre los infartos en enfermos de 35 a 40 años en comparación con los de mayor edad, y en cambio sí hay diferencia en los infartos que ocurren en menores de 35 años, se sugiere que en lo futuro los estudios del infarto del miocardio en los adultos "jóvenes" incluyan hasta el máximo de 35 años.

3. Aunque muchos de los datos referentes al infarto del miocardio en los soldados jóvenes y en veteranos es aplicable a la población en general, algunos datas que no son aplicables se han discutido.

RESUMÉ

1. Les auteurs ont comparé les infarctus myocardiques ayant frappé des malades âgés au maximum de 35 ans dans 27 cas provenant de l'hôpital des anciens combattants et dans 16 appartenant à un hôpital privé. Les différences suivantes furent notées: l'infarctus était imputable à l'artériosclérose sans maladie apparente associée dans un plus large pourcentage chez les anciens combattants que chez les malades privés, et ceci fut particulièrement vrai dans les cas à issue fatale: sur le total des infarctus la part appartenant à de jeunes adultes fut plus importante à l'Hôpital des anciens combattants qu'à l'hôpital privé; dans un quart de ces cas qui comprenait les deux sexes, il s'agissait de femmes.

2. L'étude des travaux sur l'infarctus myocardique des malades âgés de 36 à 41 ans le montre semblable à celui qui frappe les malades plus âgés et différent de celui des malades âgés de 35 ans au maximum. Les auteurs suggèrent en conséquence que dans les études ultérieures sur l'infarctus myocardique survenant chez de "jeunes" adultes, l'âge maximum de cette catégorie soit de 35 ans.

3. Bien que beaucoup des constatations concernant l'infarctus myocardique chez de jeunes soldats et anciens combattants soient applicables à l'affection constatée dans la population générale, les auteurs en ont mis en évidence certaines qui se différenciaient.

ZUSAMMENFASSUNG

1. Ein bei Kranken im Alter von 35 Jahren oder weniger auftretender Herzinfarkt wurde verglichen mit 27 Patienten eines Kriegsversehrten-Krankenhauses und 16 Patienten eines zivilen Krankenhauses. Es wurden folgende Abweichungen festgestellt: Der Infarkt war in einem grösseren Prozentsatz die Folge einer Arteriosklerose ohne andere damit verbundene Krankheiten bei den Wehrmachtsangehörigen als bei den zivilen Patienten; dies traf ganz besonders zu für die tödlichverlaufenden Fälle; ein grösserer Anteil an der Gesamtzahl der Infarktfälle betraf jüngere Erwachsene des Versehrtenkrankenhauses als im privaten Krankenhaus. Ein Viertel der beide Geschlechter umfassenden Reihe waren Frauen.

2. Nachdem die wiedergegebenen Veröffentlichungen über den Herzinfarkt bei Kranken im Alter zwischen 36 und 40 Jahren ähnlich denjenigen bei älteren Kranken zu sein scheinen und von Kranken im Alter von 35 Jahren und weniger abweichen, wird erwogen, dass bei zukünftigen Untersuchungen von Kranken mit Herzinfarkt im Alter von 35 Jahren und weniger das Höchstalter 35 Jahre betragen sollte.

3. Obwohl eine grössere Reihe von Angaben über den Herzinfarkt bei jungen Soldaten und Versehrten auch für diese Erkrankung bei der Gesamtvevölkerung gilt, werden einzelne Beobachtungen besprochen, für die dies nicht zutrifft.

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Role of the Pacemaker in the Therapy of Complete A-V Heart Block, Stokes-Adams Seizures and Episodes of Cardiac Arrest

The purpose of this presentation is to discuss briefly the present role of the pacemaker in the therapy of complete A-V heart block, Stokes-Adams seizures and episodes of cardiac arrest, and to clarify some of the misconceptions concerning its use.

Complete A-V Heart Block

In the asymptomatic variety of complete A-V heart block (absence of syncopal attacks or congestive failure) no therapy is required to increase the ventricular rate. In the symptomatic variety (associated with syncopal attacks and/or congestive failure) procedures are indicated to increase the ventricular rate. This may be accomplished by the use of sympathomimetic drugs (ephedrine, Isuprel) and/or molar sodium lactate. Following operative correction of interventricular septal defects, complete A-V heart block occasionally occurs because of the interruption of the A-V conduction system. Heart failure and/or Stokes-Adams seizures are frequent complications. In such instances the use of the pacemaker as a temporary expedient may be helpful in increasing the cardiac rate. The resulting increase in cardiac output will have a salutary effect on the congestive failure and will prevent Stokes-Adams seizures.

Stokes-Adams Disease

Stokes-Adams disease is characterized by the development of syncopal attacks and/or convulsive seizures due to failure of the heart to deliver blood to the brain for a period ranging from 3 to 9 seconds. The cardiac mechanisms during the attack consist of the following: ventricular flutter, ventricular fibrillation, ventricular standstill and cardiac arrest of the entire heart (auricles and ventricles). These may occur alone or in various combinations.

The cardiac mechanism in between attacks is usually that of complete A-V heart block. Occasionally, however, sinus rhythm (with a normal or prolonged P-R interval) may be present. In these instances the attacks result from a failure of the ventricular pacemaker to take over ventricular beating during the transition stage from partial to complete A-V heart block. In some cases the episodes of cardiac standstill may be a manifestation of the cardio-inhibitory type of carotid sinus syncope. This may occur either as the sole mechanism or in association with the vasodepressor type of syncope.

Treatment of the Stokes-Adams Attacks

The treatment of the Stokes-Adams seizures consists of the use of certain drugs, and various mechanical and electrical devices. During the acute attack a thump on the precordium may restore cardiac beat-

ing. The drugs that are useful in increasing cardiac rhythmicity include epinephrine, Isuprel and molar sodium lactate. The first two may be given intramuscularly, intravenously or by intra-cardiac injection. Molar sodium lactate may be given intravenously or by intra-cardiac injection. In between attacks Isuprel may be given subligually, or ephedrine sulfate orally. The patient should be studied as soon as possible in order to determine the precipitating factors responsible for these seizures. These may consist of excessive exertion, excitement or electrolyte imbalance, particularly a low pH and/or hypertoptassemia. The use of the above measures is frequently efficacious in the treatment or prevention of further seizures.

Use of the Pacemaker in Therapy

Pacemakers Available: The pacemakers available consist of: (a) certain external pacemakers which are applied over the precordium and have a voltage that ranges from 25 to 150 volts; and (b) internal pacemakers* which require a small current source because they are directly connected with the heart muscle.

Indications for the Use of Pacemakers: A. The external pacemaker may be used in patients with Stokes-Adams seizures and cardiac arrest. It is often effective in restoring cardiac beating where the period of asystole is relatively short (less than a minute). It has the advantage in that it may be applied by a nurse or other non-professional personnel. It has the disadvantage of producing contractions of the pectoralis and neighboring muscles, and of occasionally causing burns. Also, the external pacemaker cannot usually be applied in children.

B. The internal pacemakers which are available are transistorized, small in weight and have a range of current as follows: from 1 to 24 milliamperes and from 1 to 15 volts. A small amount of current (1 to 4 milliamperes) is usually effective. The internal pacemaker may be used in the following conditions: (1) when drug therapy is ineffective or only partially effective; (2) when attacks occur frequently, for example, 5 or 6 in one day; and (3) following cardiac arrest. During thoracic and other operations the pacemaker may be attached as soon as massage restores cardiac beating. By so doing, it will diminish trauma to the heart as well as fatigue of the operator.

The advantages of the internal pacemaker are as follows: It requires relatively little current; it eliminates contractions of the pectoralis and other muscles; it is not associated with burns to the heart or precordial region; it is small and light in weight, about two pounds and can easily be carried about by the patient. The Atronic Unit has the added advantage in that it is a current, not a voltage source, with automatic adjustment made by the instrument for increase in impedance. The following types of application are available: In the acute stage the unit may be attached in a period of less than a minute by piercing the chest wall with a needle through which is passed a fine wire which makes contact with the heart. For chronic stimulation over a period of days and weeks, the wire may be sewn directly to the heart muscle through a small

*Monitor Pacemaker, General Atronics, Bala Cynwyd, Penna.
Metronic Unit, Minneapolis, Minn.

thoracotomy incision, or may be inserted through a catheter, which is passed into the external jugular vein, and whose proximal portion is situated at the outflow tract of the right ventricle. The internal pacemaker so attached has produced effective cardiac stimulation for periods as long as 10 weeks.

Limitations of the Use of the Pacemaker: The pacemaker may restore cardiac beating with the production of effective ventricular contractions when the integrity of the heart muscle has not been unduly impaired; when the degree of anoxia is slight; when the period of cardiac arrest is relatively short, for example, less than 30 seconds and not more than a minute; and when the Stokes-Adams episode is not accompanied by circulatory (peripheral) failure. *The pacemaker is not a substitute for thoracotomy and cardiac massage.* Thoracotomy, cardiac massage, positive pressure oxygen and all of the other methods of treating cardiac arrest should be instituted in the presence of circulatory failure or periods of cardiac arrest prolonged over one minute. One should be cautious in the use of the pacemaker in the two latter conditions, lest the precious time necessary for the ideal performance of cardiac resuscitation be lost.

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SAMUEL BELLET, M.D., F.C.C.P.*
Philadelphia, Pennsylvania

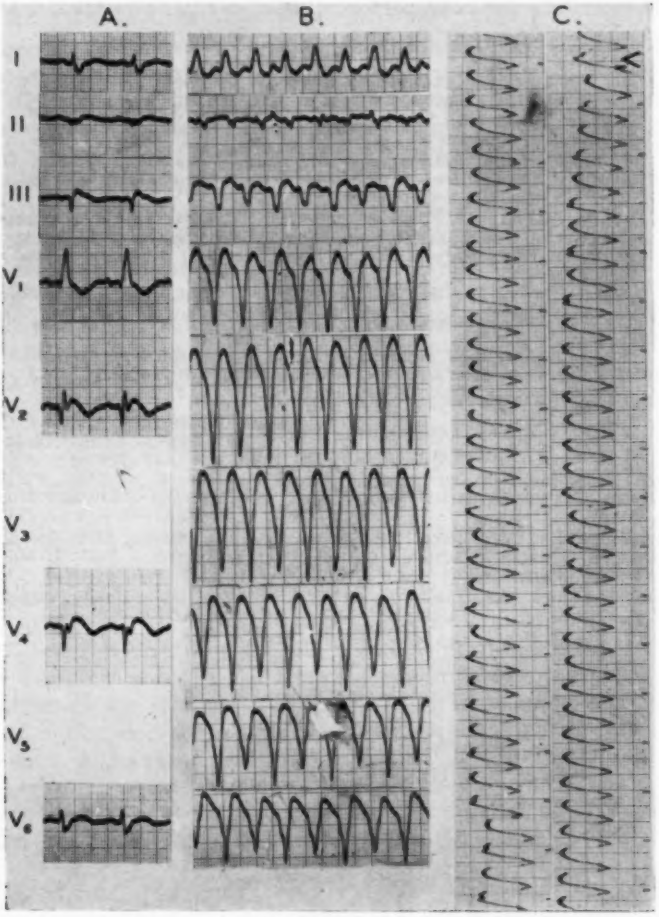
From the Department of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania, and the Robinette Foundation of the University of Pennsylvania, Philadelphia, Pennsylvania.

*Director, Division of Cardiology, Philadelphia General Hospital; Director, Division of Cardiovascular Diseases, Graduate Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

This work was aided by a grant from the United States Public Health Service, Grant H141 (C8), and the Eli Lilly Company, Indianapolis, Indiana.

THE ELECTROCARDIOGRAM OF THE MONTH

A man age 62 who had sustained a previous myocardial infarction was first seen with bronchopneumonia and congestive heart failure. When these had responded to proper treatment the electrocardiogram *A* was recorded. Right bundle branch block and the signs of diaphragmatic and antero septal infarction are evident. As he was about to be discharged from the hospital he developed rapid heart action and electrocardiogram *B* was recorded. The question as to whether this was a ventricular tachycardia or a supraventricular tachycardia with bundle branch block arises but in this case is settled in favor of ventricular tachycardia. The reasons are that previous records established the fact that he had had right bundle branch block for some time and therefore this lesion was probably permanent. The form of the record B would infer that left bundle branch block was present. If a supraventricular tachycardia produced



left bundle branch block and right bundle branch block was already present, complete A-V block should have resulted.

The most reliable criterion of ventricular tachycardia is the presence of a recognizable independent auricular rhythm, such as is shown in record *C* from another patient. This finding is also suggested in Lead II of record *B* but was considered inconclusive because the ventricular complexes were small and the variations might have been due in part to changes in intraventricular conduction of which there is ample evidence; note the well marked electrical alternation especially evident in the left precordial leads.

MANUEL GARDBERG, M.D. and
IRVING L. ROSEN, M.D., F.C.C.P.*
New Orleans, Louisiana

*Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

Clinical Information

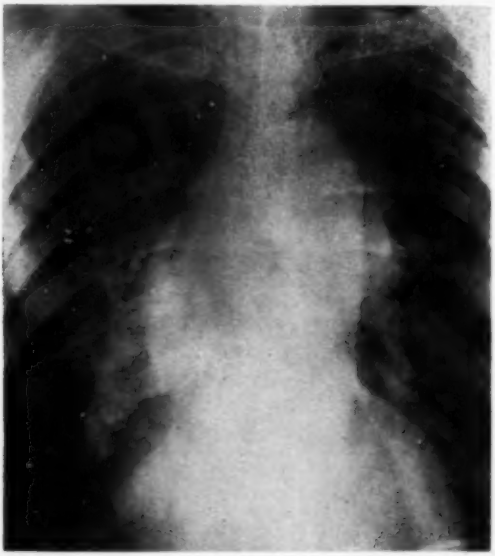
This 71 year old negro was admitted to the hospital in a comatose state. Physical examination showed him to be markedly dyspneic and cyanotic, with peripheral venous distention. There was decreased respiratory excursion on the right side, where breath sounds were notably decreased. There was a past history of bouts of congestive heart failure and recurrent pneumonia.

Answer: PULMONARY ARTERY THROMBOSIS, RIGHT

Autopsy revealed a large well-organized firmly adherent thrombus in the right main pulmonary artery. Pulmonary arterial sclerosis was found throughout both lungs. The right ventricle was markedly dilated and the left ventricle hypertrophied

Roentgenographic examination of the chest, as demonstrated in the present case, shows a distinct decrease in the vascularity of the affected lung, a prominent main pulmonary artery segment, and enlargement of the thrombosed hilar artery, which appears to terminate abruptly. These roentgen findings are considered to be characteristic of pulmonary artery thrombosis. Principal symptoms and signs include those of congestive heart failure, dominated by dyspnea, peripheral edema and cyanosis. The electrocardiogram is indicative of cor pulmonale.

Although acute pulmonary artery thrombosis is a well-recognized entity, chronic thrombosis is rarely diagnosed. The latter condition usually is superimposed on underlying disease of the lungs, heart or pulmonary vessels which may mask the occlusive phenomenon. Massive thrombosis may either be superimposed upon a previous pulmonary embolus or arise *de novo*. Among the precipitating factors, chronic passive congestion of the lungs secondary to heart disease is one of the



more important. Others include localized pulmonary arterial disease secondary to syphilis; pulmonary tuberculosis, sarcoid or carcinoma; congenital heart disease, such as tetralogy of Fallot, septal defect, patent ductus arteriosus or congenital dilatation of the pulmonary artery; acquired heart disease such as mitral stenosis and bacterial endocarditis; and polycythemia vera, thrombo-angiitis obliterans of the pulmonary artery and chest trauma.

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HAROLD POMERANTZ, M.D.
Cincinnati, Ohio

Resident, Department of Radiology, University of Cincinnati College of Medicine

Acute, Diffuse, Interstitial Fibrosis of the Lungs

REPORT OF A CASE

F. J. SANEN, M.D.,* R. D. BUSIEK, M.D.,** and H. A. JOHNSON, M.D.†
Taunton, Massachusetts

The syndrome of acute, diffuse, interstitial fibrosis of the lungs, first described by Hamman and Rich in 1935[1] and 1944,[2] is still essentially unaffected by therapy and obscure in etiology, despite its rather distinctive clinico-pathological picture. A recent review analyzes all of the previous case reports and treats extensively the possible etiologies.[3] However, in view of several remarkable features, it was felt worthwhile to present briefly this one additional case. These include a 19-year hospital confinement for mental illness with consequent opportunity for close observation, an unusual combination of laboratory and pathological findings, and a strikingly rapid onset and short course documented by chest films.

The case which follows bears a close similarity to those of Hamman and Rich, both clinically and histologically, and particularly in its brief duration. Their four patients had unexplained cough and dyspnea, while other symptoms were minimal, and all died of pulmonary insufficiency and/or right heart failure from 31 days to six months after the onset of symptoms. The characteristic pathological changes in the lungs were: (1) Edema and fibrin deposit in alveolar walls followed by extensive, diffuse interstitial proliferation of fibrous tissue; (2) enlargement of alveolar lining cells; (3) minimal leukocytic infiltration; (4) necrosis of alveolar and bronchiolar epithelium; and (5) alveolar hyaline membranes.

The illness as described in the original cases, and also in a relatively few others, including the present one, can properly be called "acute." This is in contrast to a majority of the reports, which are concerned with courses of years in duration.

Case Report

A white widowed woman, a former domestic, was admitted to Taunton State Hospital (case No. 33642) in July of 1938 at the age of 62 because of agitated behavior in response to hallucinations. She remained hospitalized for 19 years, with her fatal illness occurring at age 81. She was diagnosed as suffering from psychosis with cerebral arteriosclerosis, and initial therapy was aimed at controlling overactivity. Later, she was generally pleasant and cooperative, with a much clearer sensorium; she no longer reacted to hallucinations, but indulged only in occasional temper tantrums. There was history of cancer in two sisters; her own medical history was marked by an oophorectomy, said to be for an ectopic pregnancy. Admission physical examination and laboratory determinations did not indicate any noteworthy physical illness. Mild diabetes mellitus was manifested within two years after admission. An epidermoid carcinoma was removed from the left hand nine years after admission and a benign intraductal papilloma from the right breast about four and one half years later. She was given intermittent "cardiac" therapy for an illness said to be characterized by "hepatomegaly, ascites and peripheral edema," but had required no such treatment for the past 15 years.

*Chief, Medical Service, Taunton State Hospital. Presently at Hicksville, New York.
**Assistant Physician, Medical Service, Taunton State Hospital. Presently at Boston, Massachusetts.
†Pathologist, Department of Pathology, Pondville Hospital. Now at Brookhaven National Laboratory, Upton, New York.
From the Department of Medicine, Taunton State Hospital, Taunton, Massachusetts, and the Department of Pathology, Pondville Hospital, Walpole, Massachusetts.

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 1: Posteroanterior x-ray film, one year before final illness (December 12, 1956). FIGURE 2: Posteroanterior x-ray film on the third day of final illness (December 12, 1957). FIGURE 3: Posteroanterior x-ray film on the 14th day of final illness (December 23, 1957).

Her first chest film, taken four years after admission, showed no evidence of pulmonary disease. The heart showed left ventricular hypertrophy and dense calcification in the aortic arch. Just a year before her final illness, another film again showed normal lung fields (Figure 1). She remained asymptomatic, with diabetes well controlled, and with no other abnormality reflected by routine laboratory tests, until the onset of the final illness. A blood study a week before fever began gave a red cell count of 3,500,000 with a hematocrit of 30 per cent and a hemoglobin of 10.6 gm; and 4,300 white cells, of which 39 per cent were neutrophils, 7 per cent stab forms, 1 per cent eosinophils, and 53 per cent lymphocytes. Blood urea nitrogen was 14 mg per cent. During this period, she responded to treatment for aphthous buccal ulcers. She also had vague complaints of malaise, non-localized chest pain, and joint pain suggestive of arthritis, but without objective signs. Paget's disease of the pelvis was an incidental finding.

Her febrile illness began with a temperature of 101.2°F, and treatment included Tetracyn, 250 mg q.i.d. A white blood cell count two days after onset was 3,800 with 39 per cent neutrophils, 10 per cent stab forms, 1 per cent eosinophil, and 50 per cent lymphocytes. On the next day, a chest film was interpreted as showing only minimal congestion (Figure 2). Physical examination gave evidence of moderate hepatosplenomegaly, but was not otherwise remarkable until terminal cyanosis and pulmonary congestion developed three days before death. On the eighth day, the hematocrit was 23 per cent, hemoglobin 7.9 gm per cent, white cell count 2,300 with a full differential count not performed, but frequent primitive cells seen. Marked cyanosis and dyspnea developed on the 14th day with moist rales scattered throughout all lung fields and an x-ray film showed diffuse infiltration, appearing somewhat coarser than miliary dissemination, involving almost the entire lung fields bilaterally (Figure 3). Oxygen and digitalis were added to the treatment and bone marrow aspirated. Following blood transfusion, the hematocrit on the 15th day was 34, with white count 4,700, again including many primitive forms. A direct serum bilirubin was 2.20 mg per cent and indirect was 2.95 mg per cent.

The hematologic abnormalities dominated the early clinical considerations so that aleukemic leukemia and aplastic anemia were tentative diagnoses. With the physical and x-ray findings of pulmonary infiltration, infection, such as staphylococcal pneumonia, was felt to be associated. Hematological review of peripheral blood and marrow slides confirmed the presence of primitive white cells, but the diagnosis was felt to be aplastic depression of the bone marrow in the face of toxicity from overwhelming pulmonary disease.

A septic course continued until the final days of illness, with rectal temperatures usually reaching 102-103 daily. Diabetes remained controlled as indicated by relatively normal blood sugars. The disease was progressive, with little response to any of the therapeutic measures and she died on the 17th day after onset of fever.

Necropsy Findings

There were petechial hemorrhages of the pericardium, which was otherwise thin and transparent. The heart weighed 380 grams. None of the heart chambers was dilated, and the right and left ventricular walls were 4 mm. and 12 mm. thick, respectively. There was no hemorrhage, softening, or fibrosis of the myocardium. Microscopically there was fatty infiltration of the myocardium. Except for slight calcification of the aortic valve, the valve leaflets were thin and pliable. There was minimal atherosclerosis of the coronary arteries.

There was no free fluid in either pleural cavity. The lungs weighed 940 and 760 grams. The pleural surfaces were dull with small patches of fibrin on them. All pulmonary tissue was diffusely subcrepitant with a firm, unyielding consistency, and on sectioning was uniformly light gray. The histologic appearance was striking, giving an overall impression that the entire lung parenchyma was rapidly turning into fibrous connective tissue. Alveolar septa were thickened and contained proliferating fibroblasts, lymphocytes, and neutrophilic polymorphonuclear leukocytes (Figure 4). Eosinophils were not numerous. In some alveolar walls there were already mature collangen fibers in association with fibroblasts. Alveolar lining cells were greatly hypertrophied and had large, vesicular nuclei. Many of these had exfoliated into the alveolar spaces, and some showed phagocytic activity. Most of the alveoli contained only these bizarre cells, but a few contained clumps of fibrin in various stages of resolution. There was no cellular intra-alveolar exudate, nor were there hyaline membranes. There was no exudate or aspirated material in the bronchi. There were no emboli in pulmonary arteries. An enlarged mediastinal lymph node showed extensive caseation necrosis, epithelioid reaction, and Langhans giant cells. Tubercles were not found in the lung parenchyma.

There was no free fluid in the peritoneal cavity. The liver weighed 1310 grams. Its surface was finely nodular and the parenchyma had a "nutmeg" appearance. Microscopically there was moderate degenerative fatty infiltration of the central portions of the lobules. Multiple sections of liver disclosed two microscopic non-caseous tubercles.

The spleen was soft and enlarged, weighing 205 grams, and the pulp was infiltrated by polymorphonuclear leukocytes. The kidneys weighed 120 and 140 grams and their surfaces were granular. There was hyaline fibrosis of occasional glomeruli and ad-

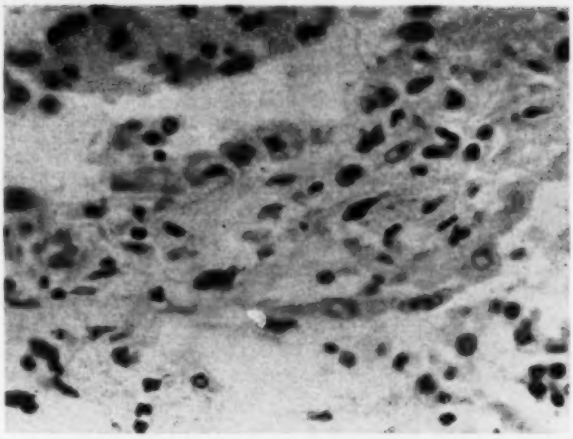

FIGURE 4: A characteristic alveolar septum showing the hypertrophied alveolar lining cells and the thickening by edema, fibroblasts, and occasional inflammatory cells.

vanced intimal thickening of small arteries. There was a small endometrial polyp. Ovaries were absent. The vertebral bone marrow was slightly paler than usual. Other organs showed no abnormality.

The principal pathologic diagnoses were:

(1) Acute, diffuse, interstitial pulmonary fibrosis with associated interstitial pneumonitis.
(2) Fibrinous pleuritis.
(3) Active tuberculosis of mediastinal lymph node with recent dissemination to liver.
(4) Acute toxic splenitis.
(5) Low grade right heart failure with chronic passive congestion of liver and edema of lower extremities.
(6) Arteriolonephrosclerosis.
(7) Endometrial polyp.

Discussion

As has been mentioned, the relatively abrupt onset and fulminant course of 17 days, believed to be the shortest on record, is consonant with the original description but in contrast to the majority of later cases.[3-19] No prior sign or symptom of pulmonary disease was evidenced. Laboratory and particularly x-ray film studies were similarly negative. The changes in chest film findings during the febrile illness were remarkable. (See illustrations). There are, however, several other reports of courses of six months or less, and recently illnesses of 29 and 25 days have been described.[3] In the more chronic form of the disease, a patient was treated with corticotropin and cortisone, with improvement to the point that an x-ray film showed reduction in a previous fairly extensive process to a few fibrous strands. After cessation of therapy, rapid exacerbation led to death in five days. The total length of illness was, of course, much greater; nevertheless, the rapidity with which the disease may progress from a few findings to a fatal outcome is again illustrated.[17]

No aplastic anemia or leukopenia has been described previously; on the contrary, a tendency toward leukocytosis and polycythemia has been variably present. The leukopenia with relative lymphocytosis and the progressive anemia with chemical jaundice apparently represented toxic depression of the bone marrow.

Also unusual was the presence of active tuberculous foci in a mediastinal lymph node, with tubercles (but probably not actual miliary spread) in the liver. Pulmonary tuberculosis has been an occasional finding, and the patient of Hamman and Rich with the shortest course had a cavity, but this has not been considered significant. A tuberculous basis for the illness in the present patient again seems unlikely.

A definite etiology has never been proved in any of the cases reported so far, and, indeed, the frequent assumption that this syndrome represents a disease entity with one etiology is unfounded.

The group of acute reactions into which the present fulminant case falls might presumably have a different cause than the more chronic group. Diffuse interstitial pulmonary fibrosis may very well be a type of non-specific reaction to a wide variety of pulmonary insults. In this respect, it could be somewhat analogous to keloid for-

mation in the skin. The tendency to react in this way may be a constitutional or familial trait, as evidenced by the occurrence of the relatively rare disease in siblings.[3,12]

In the acute group, an infectious agent is possible, although none is demonstrable. Viral etiology is perhaps the leading possibility but it remains so more by virtue of exclusion of other causes than by positive evidence. Primary atypical pneumonia may resemble this syndrome, however, and viral infections characteristically cause an interstitial inflammatory reaction, often with cuboidal metaplasia of the alveolar lining cells, and with the alveolia usually free from significant inflammatory exudate. Lack of demonstrable inclusion bodies in the Hamman-Rich syndrome is not conclusive, since they are absent in some diseases known to be viral in origin. It must be emphasized, however, that these similarities are only suggestive.

A relationship to the collagen diseases is again speculative. Fibrosis of the alveolar walls has been described in scleroderma, and reported cases of Hamman-Rich syndrome have had associated diagnoses of scleroderma and periarteritis nodosa. (These have been tentatively excluded on examples of this syndrome by some authors because of this associated collagen disease). Response to steroids, with relapse following discontinuance, in consistent with this etiology, although such result is far from uniform and may be exceptional. The frequency of associated rheumatoid arthritistis and the histological similarities to rheumatic pneumonia may be significant. Hypersensitivity reactions again may have some similar features. Reaction to a toxic agent appears less likely. It must be concluded that the syndrome remains obscure and perhaps varied in its etiology.

ACKNOWLEDGMENT: We are indebted to Dr. Fernando Rubio, Jr., New England Medical Center, for his hematological interpretation and to Mrs. Mary Parker, Medical Secretary, for her kind cooperation.

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Bronchial Adenoma of Carcinoid Type with Distant Metastases

S. W. BERKHEISER, M.D.
Harrisburg, Pennsylvania

Bronchial adenomas comprise approximately 6 to 10 per cent of all primary neoplasms of the lung.[1] Since most adenomas are usually resectable and are potentially curable,[2] they constitute an extremely important group both from the pathologic and clinical viewpoints. Many aspects concerning their histology and clinical course, however, are still controversial.

Most authors agree with the subdivision of the broad general group into two main types: (1) the cylindroid, or cylindromatous form; (2) the carcinoid form. Considering the large number of bronchial adenomas reported, it is surprising to find only a few with distant or disseminated metastases. Survey of the available literature reveals that the adenomas producing distant metastases have been almost exclusively of the cylindroid type. During a recent study a most unusual case of the carcinoid form with distant metastases was observed. Because of the rarity it is believed worthy of presentation.

Case Report

The patient was a 73 year-old white man admitted to the hospital November, 1950. His presenting complaint was low back pain of two years duration. Except for slight ankle edema of several months duration, no other symptom was noted.

Physical examination disclosed a temperature of 100° F; pulse rate-100; respiration rate-20; and blood pressure 136/80. The physical findings were rather meager. A few expiratory rales were audible over both lung bases. There was slight edema of the extremities.

The red cell count was 3.72 million with 12.0 gm. of hemoglobin. The white blood cell count was 14,200, with a differential of 89 neutrophils, and 11 lymphocytes. Urinalysis disclosed 4 plus albuminuria, with a few red and white cells on microscopic examination. Other laboratory data including serology, carbon dioxide content, chloride determination, urea nitrogen, and electrolyte studies were within normal limits.

A chest roentgenogram disclosed an oval tumor mass in the anterior segment of the right upper lobe. Slight compression of the body of the 11th thoracic vertebra, possibly due to old fracture, was also noted.

Treatment consisted of intravenous supportive measures, combined with penicillin administration.

His clinical course was characterized by stormy episodes of pulmonary edema with marked dyspnea. In spite of the usual therapeutic measures, he failed to improve, and he expired about one week after admission.

Pathology

Gross Autopsy Findings: Only the significant postmortem findings are recorded.

Approximately 150 cc. of clear yellow fluid was present in the right pleural cavity. The right pleural space was virtually obliterated by dense fibrotic adhesions. The weight of the right lung was 995 grams, and that of the left lung 500 grams. The entire tracheo-bronchial tree contained a large amount of thick yellowish mucus. Just within the main stem bronchus of the right upper lobe was an oval, 1.5 cm. mass, which produced almost complete bronchial obstruction (Fig. 1). The

From the Department of Laboratories, Harrisburg Polyclinic Hospital.

surface was fairly homogenous, gray-white, and slightly lobulated. The lesion was not encapsulated and there was apparent extension into the adjacent lung parenchyma for a distance of 2.0 cm. The right upper lobe distal to the tumor showed evidence of prolonged obstructive changes with some cavitation and numerous dilated bronchioles. The right and left lower, as well as the right middle lobes showed extensive confluent bronchopneumonia.

The liver was enlarged and weighed 4000 grams. The entire parenchyma was studded with metastatic nodules varying from 1 to 8 cm. in diameter. An estimated 80 per cent of the liver tissue was replaced by the metastatic nodules.

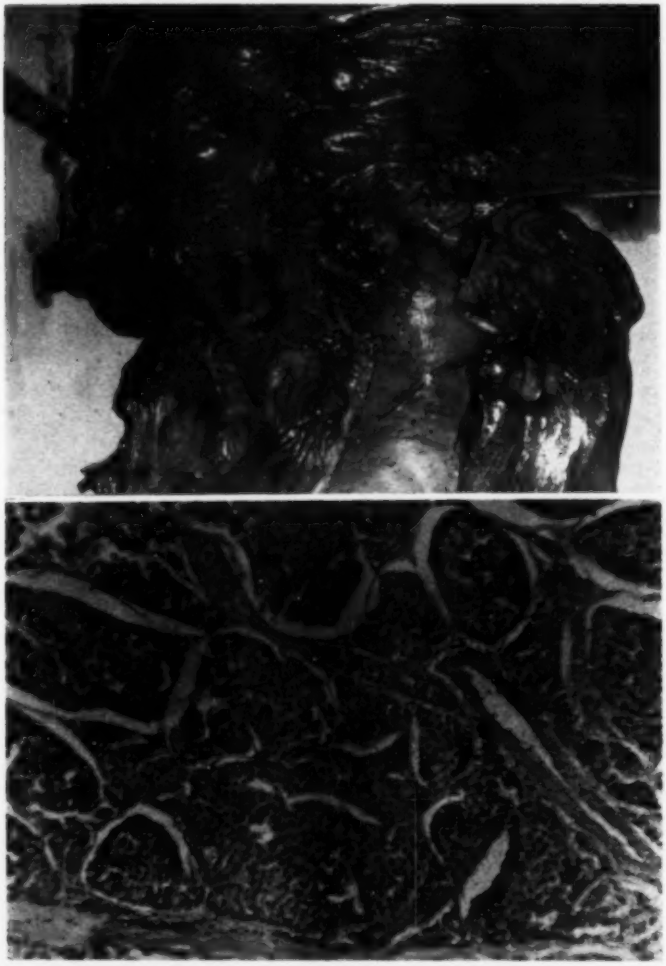

FIGURE 1: Gross photograph showing bronchial adenoma arising in main bronchus of right upper lobe.

FIGURE 2: Photomicrograph disclosing the organoid pattern of bronchial adenoma of carcinoid type. Note the regular cell outlines and the lack of mitotic activity (x 160).

Both kidneys were moderately enlarged and contained grayish-white nodular implants, averaging 0.5 cm. in diameter.

Moderate enlargement of the regional hilar lymph nodes was also observed. Multiple metastases were also present in the right fourth, fifth, seventh ribs, the left sixth rib, and the lower thoracic vertebrae.

Microscopic Findings: The bronchial neoplasm was composed of groups of small regular cells with a cuboidal or slightly elongated outline. The nuclei were uniform, oval, and abnormal mitotic figures were rare. There was a definite tendency to form small cords with an intervening fibrous stroma, which was thin and delicate. The cellular pattern was of a definite organoid type and closely resembled that of a carcinoid tumor (Fig. 2). Clumps of similar cells were present within the submucosal lymphatic vessels of the submucosa of the bronchus. None of the features was typical of the cylindromatous variety of bronchial adenoma. Other sections of right lung showed extensive pneumonitis of obstructive type. The left lung showed similar changes, but to a less marked degree.

The metastases present within the hilar lymph nodes, liver (Fig. 3), kidney (Fig. 4), and bone showed a virtually identical histologic pattern as the primary lesion within the right upper lobe.

Discussion

The natural history of bronchial adenomas indicates they are predominately slow-growing neoplasms, regional metastasis being observed in about 5 to 10 per cent of the cases.[3] According to the literature, the cylindroid type of adenoma is more invasive microscopically than the carcinoid form.[1] The potential malignant capacities of these two main types is subject to some dispute.

Until 1937, there had been no report of a case of adenoma with metastasis.[4] By 1943, several cases with metastasis to adjacent lymph nodes, or microscopic metastases in the vertebrae and liver, had been recorded. Cases of adenoma with metastases have been described by Anderson,[4] Graham and Womack,[5] Geever and others,[6] and by Soutter, Sniffen, and Robbins.[7] As far as can be determined from the photomicrographs and descriptions of these cases, all of the adenomas producing distant metastases have been of the cylindromatous type. In some of the reported cases, the exact classification is uncertain. One of the cases described by Graham and Womack simulated the carcinoid form, but the neoplasm also contained sarcomatous-like components. Liver metastasis was observed in this particular case. Soutter and others studied one of the largest series of bronchial adenomas reported to date. After studying a group of 56 adenomas of carcinoid type and four of cylindromatous type, they concluded that the cylindromatous variety were much more malignant in behaviour than the carcinoid forms. No distant metastases, however, were noted in either group. Metastases in the carcinoid group were restricted primarily to the regional lymph nodes, and none was considered inoperable.

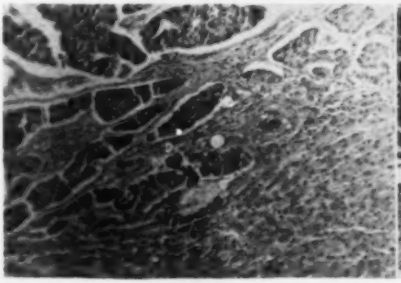

FIGURE 3

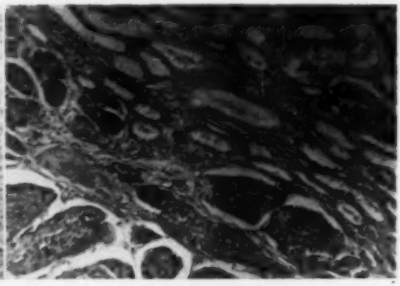

FIGURE 4

FIGURE 3: Photomicrograph showing details of liver metastasis (x 160). FIGURE 4: Photomicrograph of renal metastasis. Note the simularity to original bronchial tumor.

From study of the present case, none of the microscopic features was of aid in determining whether generalized metastases could be expected. The histology was identical with numerous cases previously reported as the benign carcinoid type of bronchial adenoma. The situation is analagous to the problem of the differentiation of benign and malignant tumors of endocrine gland origin, particularly those derived from the adrenal medulla. Unfortunately, the presence of metastases is the only reliable criterion of malignancy, since the histologic features of the benign and malignant forms may be quite similar.

It is well to emphasize that the incidence of metastasis in the bronchial adenoma group is low compared to other malignant pulmonary tumors. More patients will die of obstructive pneumonitis or hemorrhage than from metastases. The extensive study of McBurney, Clagett, and McDonald[3] established this fact beyond any reasonable doubt.

Since the histologic differentiation of benign and malignant types of bronchial adenoma may present problems, it is logical that early diagnosis and adequate surgical removal offers the best opportunity for long term survival.

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The Effect of Intravenous Paraldehyde as Recorded by the Chest X-Ray Film

A Case Report*

LT. JEROME A. GOLD, MC, USNR,** LT. ROBERT C. GARCIA, MC, USN, and LT. JOHN W. DAVIS, MC, USN
Bethesda, Maryland

The administration of paraldehyde by the intravenous route is rarely, if ever indicated. Burstein[1] reported a death five hours following the intravenous injection of 33 cc. of paraldehyde.

Earlier reports revealed deaths from the oral administration of 35, 75, and 120 cc.[2,3] and from the rectal administration of 12 and 31 cc.[3,4] of paraldehyde.

The following case demonstrates the unusual pulmonary manifestations after the intravenous use of only 5 cc. of paraldehyde. The patient's chest x-ray film is considered a medical rarity, as well as indicative of the underlying pathology.

A 21 year old white man was admitted to the medical service of the U. S. Naval Hospital, Bethesda, Md. after he had previously received 5 cc. of paraldehyde by the intravenous route. Following the injection, which was given for hyperexciteability, he experienced a short period of apnea, severe cough, tachycardia, and hypotension. Past history, family history, and review of systems were unremarkable.

On admission to the ward (30 minutes after the injection) physical examination revealed blood pressure 130/90, pulse rate 88 per minute, and respirations 18 per minute. He was in deep sleep. Both lung fields revealed distant breath sounds with occasional coarse rhonchi. The remainder of the examination was within the limits of normal.

Laboratory studies revealed a white blood count of 14,650 with 74 per cent neutrophiles and hemoglobin 17.4 gms. Sedimentation rate and urinalysis were normal.

Admission chest x-ray films (Figures 1a, 1b, 1c) revealed bilateral increase in bronchovascular pattern. Scattered throughout both lung fields were multiple small nodular densities compatible with pulmonary edema and congestion.

An x-ray film (Figures 2a, 2b) taken 36 hours later showed complete clearing of the pulmonary pathology and was within normal limits. He was now asymptomatic, afebrile, and fully ambulatory. The lung fields were normal to percussion and auscultation. Therapy consisted solely of supportive measures.

Comment

Paraldehyde fatalities were originally attributed to a nebulous increased susceptibility of the individual patient.

While it is true that there is increased danger in the use of paraldehyde in cases with hepatic disease and pre-existing pulmonary disease,[7] the experiments of Burstein[1] convincingly demonstrated the primary pulmonary effects of this drug following intravenous doses.

His animals showed acute pulmonary edema with massive hemorrhages in both lungs, acute dilatation of the right heart, and edema of the viscera. Similar pulmonary findings were noted in the autopsied cases of Shoor[5] and Kotz et al.[6]

Our patient's initial chest x-ray film records the pulmonary edema and congestion and probable slight cardiac dilatation after 5 cc. of intravenous paraldehyde (Figures 1a, 1b, and 1c).

One can therefore comprehend the resultant apnea, cough, cyanosis, and tachycardia. A fatal outcome can likewise be visualized with larger doses of paraldehyde.

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*From the Departments of Medicine and Radiology U. S. Naval Hospital, National Naval Medical Center.
The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department of the naval service at large.
**Presently at Brooklyn, New York.

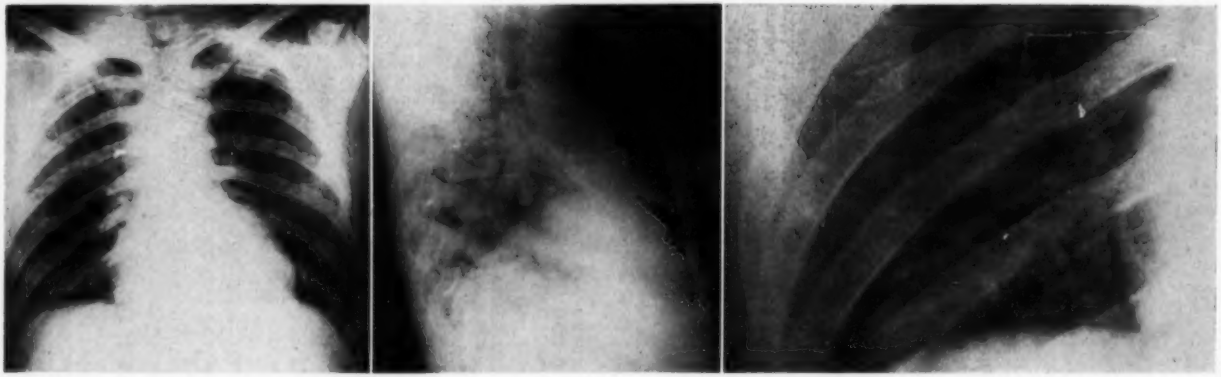

FIGURE 1a: Admission chest x-ray film showing multiple pulmonary nodular densities and probable cardiac dilation.

FIGURE 1b: Lateral projection of admission chest x-ray.

FIGURE 1c: Blowup of right lower lung field depicting the changes compatible with pulmonary edema and congestion.

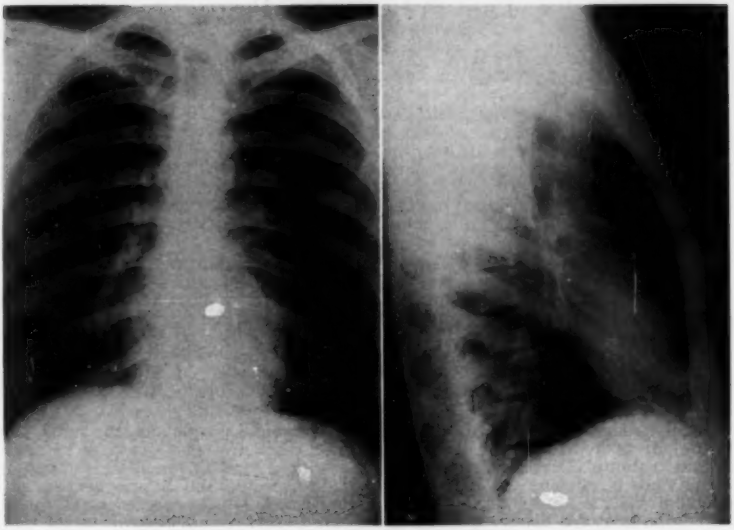

FIGURE 2a: Lateral view of chest taken 36 hours after initial chest x-ray—within normal limits.

FIGURE 2b: PA view of chest taken within 36 hours after initial chest x-ray—within normal limits.

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The President's Page

DIAGNOSIS — THE ART OF MEDICINE

A very wise and a very humble diagnostician at one of our leading medical centers used to insist that he had the easiest job in medicine. According to his account, he seldom saw a patient before all possible erroneous diagnoses had been made and disproved by subsequent therapeutic failure. He, then, had the comparatively simple job of determining what the correct diagnosis should be by considering what possibilities had been overlooked in earlier attempts. Since all the obvious diagnoses had been eliminated by trial and error, it was a comparatively simple matter, he asserted, to come up with the right one.

This is of course too humble an account of the function of the specialist in diagnosis, but it is not utterly false. It only exaggerates certain pertinent truths. In the first place, diagnosis is the one responsibility that devolves upon every physician. Specialists in diagnosis can only be an adjunct, because the most difficult diagnostic question, and often the most crucial one, is asked of the first physician the patient sees — do the patient's symptoms suggest a serious ailment, justifying exhaustive diagnostic procedures? Every physician, in the nature of things, must answer this kind of question every day in the week, and without the aid of the specialist. Ideally, then, every physician should be a specialist in diagnosis.

Secondly, diagnosis is and always has been, for most physicians, the most difficult thing they are asked to do, because it is the thing they are least fitted for by temperament and training. Diagnosis at least begins with a kind of speculation much of the time, and most physicians are by nature opposed to speculation. Simply because the end they have in view is always action of one kind or another, they are necessarily practical men. The nature of a disease process is for most of us of much less interest than the remedy for it, and we can take a reasonable amount of satisfaction in curing a disease which we did not completely identify. This characteristic is clearly seen in medical publications; medical journals are far and away the most empirical of scientific publications. This bent is both necessary and good — but it makes diagnosis difficult.

This practical bent is made manifest and confirmed by the approach to disease ordinarily taken in medical literature, and in particular in medical textbooks. There is a pronounced tendency to describe disease "practically" — to confine one's attention to its general appearances, by tabulating symptoms in order of frequency and so forth. The result is a static and perhaps unnecessary oversimplified conception of disease, adequate for treatment but deficient so far as diagnosis is concerned.

Because a disease is not a collection of signs and symptoms, nor is it static. A disease is a dynamic process; it is a war. It originates in some type of extrinsic interference with normal function, or by a specific physiologic malfunction. Hence it has a cause, or causes, which can be treated. But the manifestations of disease are habitually complicated by the fact that they are the product of additional unpredictable forces — the pathogen, for example, which may vary in virulence, and the body's defenses against it, which certainly do show a great deal of variation from one instance to the next. Hence disease must be approached as an abnormal physiological process, and to approach it from any less "theoretical" point of view is to risk error.

Nor has medical progress in the last 20 years made diagnosis any less of a problem. Indeed, since new therapies have been most outstandingly successful against those disease processes, such as pneumonia, which present the most regular appearances, they have perhaps made the diagnostic problem more acute. Most of the serious illnesses which beset modern man are not predictable in symptomology or appearance; they are disease processes which are only intermittently and unpredictably visible. Hence the physician is rather in the position of the blind men trying to define the elephant by the arm or trunk they happened to seize. He is confronted with a foot, a tail or an ear and asked to at least guess the presence of an elephant.

At the same time, diagnostic skill is perhaps the most satisfying aspect of medicine, since it makes its demands upon all the skill and powers of the diagnostician. The process of making a diagnosis begins with the command of a most technical body of knowledge, the knowledge of dynamic physiology. Then there is the search for secondary evidence of disease, for anything that might help the physician perceive the pattern of process. Finally there must be the constructive act by which all of the evidence is brought into relationship by an explanation — the diagnosis. At times it is rather like playing bridge with a pinochle deck against an opponent who makes his own rules. But in the difficulty lies the challenge which no physician can decline.

Seymour M. Farber

CHAPTER NEWS

ALABAMA CHAPTER

The annual meeting of the Alabama Chapter will be held at the Admiral Semmes Hotel, Mobile, on April 20. The program, made possible by a grant from the Merck, Sharp & Dohme Postgraduate Program, is as follows:

2:30 p. m. "Management of Emphysema"
Ben Branscomb, Birmingham
"Cough — Clinical"
Martin J. Sokoloff, Philadelphia, Pennsylvania
Diagnostic X-ray Conference: "What's My Problem?"
Neal Flowers, Mobile; Charles M. Nice, New Orleans, Louisiana; and Louis Raider, Mobile

ARIZONA CHAPTER

The Arizona Chapter will hold its annual meeting at the Safari Hotel, Scottsdale, May 5. The program is as follows:

12:00 noon "Hereditary Aspects of Pulmonary Arterio-venous Fistula"
Corrin H. Hodgson, Rochester, Minnesota
"Physiologic Aspects of Cardiovascular Surgery"
Dwight C. McGoon, Rochester, Minnesota

A business meeting of the chapter will follow the scientific session.

KANSAS CHAPTER

The annual meeting of the Kansas Chapter will be held at the Baker Hotel, Hutchinson, May 3. The following program will be presented:

Moderator: John K. Fulton, Wichita, Chapter President

1:30 p. m. "Selective Pulmonary High Carcinolytic Agent Concentration in the Treatment of Bronchogenic Carcinoma"
Alfred M. Tocker, Wichita
"Anomalous Pulmonary Veins"
C. Frederick Kittle, Kansas City, Kansas
"Clinical Caprices of Cardiac Surgery"
R. Lawrence Sifford, Wichita
"Use of Serologic Tests in the Diagnosis of Histoplasmosis"
Charles E. Andrews, Kansas City, Missouri
"Allergic Pneumonitis"
Charles Pokorny, Halstead
"Diagnostic Problems and Interesting Cases of Surgical Variety"
Robert M. Brooker, Topeka; John G. Shellito, Wichita

A social hour and dinner will follow the scientific meeting. Dr. William J. Gillespie, St. Louis, will be guest speaker at the dinner.

LOUISIANA CHAPTER

The annual meeting of the Louisiana Chapter will take place at the Nurses Home Auditorium of Our Lady of the Lake Hospital in Baton Rouge, May 1. The program is as follows:

2:00 p. m. "Massive Hemoptysis"
William Leon and Lawrence H. Strug, New Orleans
"Highlights of the 19th VA-Armed Forces Chemotherapy Conference
Howard A. Buechner, New Orleans
A Trans-Atlantic Clinical Pathological Conference — "Cardiopulmonary Diseases" (a transcription)
Richard J. Bing, St. Louis, Missouri; Brian B. Blades, Washington, D. C.; Edward S. Orgain, Durham, North Carolina and C. Thorpe Ray, New Orleans
"Mycobacterium Kansasi Infections — Consecutive Case Reports"
P. J. Ekman, New Orleans

NEW JERSEY CHAPTER

The annual meeting of the New Jersey Chapter will be held in Atlantic City, May 18, at the time of the State Medical Society meeting. Following is the chapter program:

MEDICAL — LEGAL ASPECTS OF CARDIOPULMONARY DISEASES
Chairman: Albert A. Peckman, Jersey City
Secretary: Saul Lieb, Newark

10:00 a. m. "Pathology and Toxicology of Pneumonoconiosis"
G. W. H. Schepers, Wilmington, Delaware
"Clinical Aspects of Industrial Disease"
Edgar Mayer, New York City
"Cardiac Disabilities"
Arthur Bernstein, Newark
"Legal Aspects"
Mr. Roger W. Kelly, Jersey City

Panel Discussion
Moderator: Saul Lieb, Newark
Panel: Arthur Bernstein, Mr. Roger W. Kelly, Edgar Mayer, and G. W. H. Schepers.

Dr. Andrew L. Banyai, Chicago, Illinois, will present the Sixth Selman Waksman Lecture and will speak on "Chronic Bronchitis — An Underrated Fateful Disease."

NEW MEXICO CHAPTER

The New Mexico Chapter will meet at the Western Skies Hotel, Albuquerque, on May 13 during the 78th Annual Meeting of the New Mexico Medical Society. The chapter program follows:

CARDIOPULMONARY PROBLEMS IN THE AGED
Chairman: Carl H. Gellenthien, Valmora, New Mexico
Co-chairman: Quentin Florence, Roswell, New Mexico
2:00 p. m. "Pulmonary Problems of the Aged"
Henry C. Jernigan, Albuquerque
"Cardiovascular Problems in the Aged"
Denton A. Cooley, Houston, Texas
"General Medical Problems Involving the Chest"
J. Lee Hollander, Philadelphia, Pennsylvania
Panel Discussion — "Crippling Diseases of the Chest"
Moderator: Burgess L. Gordon, Albuquerque
Panel: Denton A. Cooley, J. Lee Hollander, and Henry C. Jernigan
6:30 p. m. Social Hour
7:30 p. m. Dinner

NEW YORK STATE CHAPTER

The 20th annual dinner meeting of the New York State Chapter will be held at the Statler Hotel, New York City, May 10, in conjunction with the meeting of the New York State Medical Society. The social hour and dinner will begin at 6:30 p. m. Dr. Arthur Q. Penta, Schenectady, will present the 10th Howard Lilienthal Lecture and will speak on "The Role of Oral Infections in the Etiology of Pulmonary Suppuration."

OHIO CHAPTER

The annual meeting of the Ohio Chapter will take place in Cleveland, May 18 at the Public Auditorium, in conjunction with the meeting of the Ohio State Medical Association. The chapter program is as follows:

2:00 p. m. "Cine-coronary Angiography"
Earl K. Shirey and F. Mason Sones, Jr., Cleveland
"Present Day Status of Surgical Treatment of Aortic Stenosis"
F. L. Mendez, Jr., and Elmer R. Maurer, Cincinnati
"Structure of Normal and Emphysematous Lungs as Revealed by an Inflation and Drying Technique"
Philip Pratt, Columbus
"Effects of Bronchography on Pulmonary Function"
Joseph F. Tomashefski and Anthimos J. Christoforidis, Columbus

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter of the College and Pennsylvania Trudeau Society will meet jointly at the Bellevue-Stratford Hotel, Philadelphia, April 21. Following is the program:

Moderator: E. Wayne Marshall, Philadelphia
9:00 a. m. "Fluorescent Antibody Technique and its Application to Human Diseases"
Friedrich Deinhardt
"Use of CO_2 Tensions in the Detection of Pulmonary Emboli"
Eugene Robin, Boston
"Does Early Detection Aid Prognosis of Lung Cancer? Results of Cooperative Chemotherapy Study"
George Rosemond, Philadelphia
"Recent Advances in Cineangiography"
F. Mason Sones, Jr., and Earl Shirey, Cleveland, Ohio
"Newer Techniques in Association with Cardiac Catheterization"
Eugene Braunwald, Bethesda, Maryland
12:00 noon Joint Luncheon, Mr. Arthur Henninger presiding
"Physicians for a Growing America"
I. S. Ravdin, Philadelphia
2:15 p. m. Business meeting, College chapter
Panel Discussion — "Allergy in Relation to Pulmonary Disease"
Moderator: William Sherman
Panel: Bronchial Asthma — George Blumstein, Philadelphia
Pulmonary Function Studies in Determining the Allergic Component in Bronchospasm — Richard T. Cathcart, Philadelphia
Allergic Bronchitis — E. A. Hildreth, Philadelphia
Desensitization Technique — Mary Loveless, New York City
Conditioned Reflex in the Production of Bronchial Asthma — Perry Ottenberg, Philadelphia

BOOK REVIEW

MEDIASTINUM AND MEDIASTINAL DISEASES (LE MEDIASTIN ET SA PATHOLOGIE. In French) By Maurice Bariety, M.D., and Charles Coury, M.D., Masson & Cie., Paris, 1959. 854 pp., 312 figures, 66 tables, Fr.frs.: 11.000

During recent years there has been an amazing increase of interest in mediastinal diseases. Our means of investigation have increased in number, our knowledge on the matter thus has become more accurate and our ways of management more efficient. Until now the corresponding data were scattered in many papers but had never been gathered. The time had come to collect them in a single book. This praiseworthy task has now been carried out by Professor Maurice Bariety and Professor Charles Coury (Paris).

Having personally gathered over 240 cases of mediastinal and paramediastinal diseases, the authors give a thorough study of our present knowledge in this important field of medicine, of interest not only to the chest physician and surgeon, radiologist, and cardiologist, but also to the general practitioner.

The book is divided into seven parts with 32 chapters richly illustrated including several hundred drawings, roentgenograms and both gross and microscopic preparations.

Parts I and II may be considered introductory. Following some historical data starting with Galenus, embryology, anatomy, structure and physiology of the middle thoracic space are reviewed insofar as they interfere with mediastinal diseases. In these chapters and others, the authors often state their own experience also. Clinical and roentgenological means of investigation are then thoroughly studied; mediastinal symptoms and the so-called "pressure syndrome" are accurately and critically discussed. All x-ray procedures, including tomography, angiocardiography, and cinedensiography are described. Special consideration is given to gaseous mediastinography (artificial pneumomediastinum), a field in which the authors' personal contribution is noteworthy. The normal roentgenologic features of the middlechest shadow are fully analyzed.

Part III deals with primary tumors, mainly of surgical interest, both in adults and children. A separate chapter is devoted to each type of new growth, namely: the various homoplastic and heteroplastic tumors and cysts of embryonic origin. The first group includes bronchogenic, coelomic and gastro-enterolenic cysts, hemangiomas and lymphangiomas. The second concerns teratomas, dermoids, primary chorioepitheliomas and seminomas, as well as thoracic goiters, neurogenic and other tumors of the connective tissue. The relations between thymomas and myasthenia gravis are stressed and discussed, both in respect to their yet unclarified pathogenesis and their practical significance.

The different diseases of the lymph nodes are studied in Part IV, including primary and metastatic lymphatic tumors of all types, lymphogranuloma, sarcoidosis, tuberculous lymphadenopathy and tuberculomas of the mediastinum. Incidentally, the authors do not believe the so-called "granulomas" bear such original features as is commonly assumed. The problem of inflammatory processes (bacterial and virus infections, pneumoconiosis, etc.) and the significance of benign bilateral hilar lymphomas of undetermined origin are also discussed.

Part V is devoted to the differential diagnosis of paramediastinal tumors and tumor-like diseases, such as may involve the heart and large thoracic vessels (aortic aneurysm, etc.), the chest wall, the diaphragm, the esophagus, the pleural space, the lungs and bronchi. Mediastinal involvement by cancer of the lung is analyzed in respect to its preoperative incidence.

In Part VI, the authors deal with diseases of the mediastinal pleura and of the mediastinal tissue itself. The practice of artificial pneumomediastinum helps in understanding certain features of mediastinal emphysema. Acute and chronic mediastinitis of various origins are fully described and discussed. A special chapter is also devoted to mediastinal shifts and motions with a view toward explaining their physiology.

In Part VII, the reader will find a list of over 3,000 references, as well as a detailed index of subjects.

This valuable book is, in short, an exhaustive and successful attempt to classify, review and discuss on a personal basis all that has been written on the mediastinum and mediastinal diseases. Such a remarkable work is, as far as we know, the first in the world literature. It brings one of the steadiest and most expert contributions to modern medicine. At the present time, this book proves to be absolutely necessary to all physicians. It will also be the best book of reference for all specialists having to deal with this important field of medical science.

André Meyer, M.D.

PROGRAM

26th ANNUAL MEETING

AMERICAN COLLEGE OF CHEST PHYSICIANS

SAXONY HOTEL, MIAMI BEACH

JUNE 8-12, 1960

POSTGRADUATE SEMINARS

Wednesday, June 8

Morning Sessions — 9:00 a. m.

AM-1 PULMONARY DISEASE (MEDICAL)

Chairman:

Jack Reiss, Chief, Chest Service, Veterans Administration Hospital, Coral Gables, Florida

Chemotherapy of Carcinoma of the Lung

Ralph Jones, Jr., Professor and Chairman, Department of Medicine, University of Miami School of Medicine, Miami, Florida

Therapeutic Aids in the Management of the Patient with Chronic Pulmonary Disease

Maurice S. Segal, Director, Lung Station (Tufts), Boston City Hospital, Boston, Massachusetts

Miliary Lesions of the Lung, Diagnosis and Treatment

Charles F. Tate, Jr., Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Cardiac and Pulmonary Abnormalities in Obstructive Pulmonary Emphysema

Philip Samet, Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida

AM-2 CARDIOLOGY (SURGICAL)

Chairman:

DeWitt C. Daughtry, Assistant Clinical Professor of Thoracic Surgery, University of Miami School of Medicine, Miami, Florida

Newer Diagnostic Aids in Cardiology

Philip Samet, Associate Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Selection of Patients with Septal Defects and Patent Ductus Arteriosus for Surgery

Francisco A. Hernandez, Assistant Clinical Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Current Status of Open Heart Surgery in Treatment of Heart Disease

Robert S. Litwak, Chief, Division of Thoracic and Cardiovascular Surgery, University of Miami School of Medicine, Miami, Florida

Surgical Management of Ventricular Aneurysms

Richard G. Connar, Attending Surgeon, Southwest Florida Tuberculosis Sanatorium, Tampa, Florida

Cardiac Resuscitation

Mark W. Wolcott, Chief of Surgery, Veterans Administration Hospital, Coral Gables, Florida

Afternoon Sessions — 2:00 p. m.

PM-1 PULMONARY DISEASE (SURGICAL)

Chairman:

Hawley H. Seiler, Consultant in Thoracic Surgery, Veterans Administration Hospital (Pass-a-Grille) Tampa, Florida

The Physiological Justification for Surgery of Pulmonary Cysts and Bullae

Osler A. Abbott, Associate Professor of Surgery, Emory University School of Medicine, Atlanta, Georgia

Diagnosis and Management of Mediastinal Tumors

Francis N. Cooke, Assistant Clinical Professor of Surgery, University of Miami School of Medicine, Miami, Florida

Tracheostomies for Chronic Pulmonary Disease

Mark W. Wolcott, Chief of Surgery, Veterans Administration Hospital, Coral Gables, Florida

Postgraduate Seminars (Continued)

Modern Concepts in the Surgical Treatment of Pulmonary Tuberculosis including Atypical Forms
Ivan C. Schmidt, Clinical Assistant Professor, University of Miami School of Medicine, West Palm Beach, Florida

A ten-minute question and answer period will follow each lecture

PM-3 CARDIOLOGY (MEDICAL)

Chairman:

Marvin L. Meitus, Clinical Instructor of Medicine, University of Miami School of Medicine, Miami, Florida

Correlation of Clinical Features with Anatomic Changes in the Cardiac Conduction System
Paul N. Unger, Clinical Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Current Observations on Digitalis Intoxication
Fred Wasserman, Associate Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Failure of Correlative Serum Transaminase Levels in Some Cases of Frank Myocardial Infarction
David A. Nathan, Clinical Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Effect of Segmental Coronary Perfusion with Fibrinolysin following Acute Coronary Occlusion
Robert J. Boucek, Associate Professor of Medicine and Chairman, Department of Cardiovascular Disease, University of Miami School of Medicine, Miami, Florida

Steroid Therapy in Acute Rheumatic Pancarditis
Jim S. Jewett, Clinical Instructor of Cardiology, University of Miami School of Medicine, Coral Gables, Florida

A ten-minute question and answer period will follow each lecture

NOTE: These seminars on diseases of the chest will be presented at the Saxony Hotel on Wednesday, June 8, and are open to all physicians. The registration fee for each seminar is $7.50.

Registration for the seminars must be made in advance and accompanied by the tuition fee; seating capacity is limited and reservations will be accepted in the order received. A coupon for this purpose will be found on page 482. Please indicate your preference by number.

SCIENTIFIC PROGRAM

Thursday, June 9

8:00 p. m. — Scientific Session

Chairmen:

Seymour M. Farber, President, San Francisco, California

M. Jay Flipse, President-Elect, Miami, Florida

FIFTH LOUIS MARK MEMORIAL LECTURE

THE RELATIONSHIP OF RESEARCH TO PROGRESS IN MEDICINE

James A. Shannon, Director, National Institutes of Health, Bethesda, Maryland

A REPORT TO THE PEOPLE ON LUNG CANCER

(A motion picture of a live television presentation originally broadcast in Albuquerque, New Mexico, October 16, 1959, at the Silver Anniversary Homecoming Meeting of the American College of Chest Physicians. This telecast, sponsored by The Upjohn Company as one of a series of medical special events programs, featured members of the College as discussants).

SCIENTIFIC PROGRAM

Friday, June 10

9:00 a. m. — Scientific Session No. 1

Chairmen:
Albert H. Andrews, Chicago, Illinois
J. Winthrop Peabody, Sr., Washington, D. C.

Basic and Clinical Investigation in Diseases of the Chest

Introductory Remarks:
R. Drew Miller, Rochester, Minnesota, Chairman, Pulmonary Section, Committee on Scientific Program

Ether Excretion as a Measure of Effective Pulmonary Ventilation — A New Test of Lung Function
Theodore H. Noehren, Assistant Professor of Medicine; **Douglas S. Riggs**, Professor of Pharmacology, University of Buffalo School of Medicine, Buffalo, New York

Compliance, Resistance and the Work of Breathing in Infants
Ulrich C. Luft, Head, Department of Physiology; **Roy F. Goddard**, Director, Department of Pediatric Research; and **E. H. Reorbach**, Research Associate, Department of Physiology, Lovelace Foundation, Albuquerque, New Mexico

Observations on Alveolar-Arterial Gas Composition during Transient Mechanically Induced Hyperventilation
Joseph F. Tomashefski, Assistant Professor of Medicine and Physiology; **Earl T. Carter**, Assistant Professor of Preventive Medicine and Physiology; **Joseph A. Lupsky**, Research Assistant, Ohio State University College of Medicine, Columbus, Ohio

Effect of Respiratory Tract Obstruction Upon the Ventilatory Response to Inhaled Carbon Dioxide in Normal Subjects
Philip Samet, Director, Cardio-Pulmonary Laboratory; **Eugene M. Fierer**, and **William Bernstein**, Attending Physician in Medicine, Mount Sinai Hospital, Miami Beach, Florida

Variations in Intrathoracic Pressure and Relationship to Pulmonic Blood Flow
F. L. Mendez, Jr., Chief Surgeon, Research Memorial Heart Laboratory, St. Mary's Hospital; and **Elmer R. Maurer**, Assistant Clinical Professor of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio

Pulmonary Venoarterial Shunts in Cirrhosis of the Liver with a Note on the Existence of Peripheral Arteriovenous Shunts Across the Hands
Fouad Bashour, Paul K. Conner and **William F. Miller**, Associate Professor, Cardiopulmonary Laboratory, Department of Medicine, University of Texas Southwestern Medical School, Dallas, Texas.

Spirometric Studies in Normal Subjects: Significance of the Forced Vital Capacity
Ross C. Kory, Director, Cardiopulmonary Laboratory, Wood Veterans Hospital, Milwaukee, Wisconsin.

Simplified Pulmonary Physiology for Office Practice
Robert B. Stonehill, Lt. Colonel, USAF, MC, Chief, Pulmonary Disease Services; **Joel E. Reed, Major, USAF, MC**, Chief, Tuberculosis Service, USAF Hospital, Lackland AFB, Texas

Pulmonary Function in Cardiac Disease
Glenn E. Horton, Instructor in Medicine, University of Tennessee College of Medicine; **I. Ralph Goldman**, Senior Staff Physician, Department of Internal Medicine, Baptist Memorial Hospital and Veterans Administration Hospital, Memphis, Tennessee.

Pulmonary Function in the Selection of Patients for Open Heart Surgery
Roe E. Wells, Jr., Associate in Medicine; **Warren J. Taylor**, Assistant in Surgery; **Harrison J. Black**, Instructor in Surgery; **Dwight E. Harken**, Associate Clinical Professor of Surgery, Harvard Medical School, Boston, Massachusetts

Pulmonary Aspects of Lupus Erythematosis
Donato Alarcon-Segovia, Hospital de Enfermedades de la Nutricion; **Donato G. Alarcon**, Medical Director, Sanatorio San Angel, Mexico City, Mexico

9:00 a. m. — Scientific Session No. 2

Chairmen:
Donald E. Cassels, Chicago, Illinois
Robert F. Ziegler, Detroit, Michigan

Introductory Remarks:
Thomas W. Mattingly, Washington, D. C., Chairman, Cardiovascular Section, Committee on Scientific Program

Metabolic Cardiopathy: Acquired Heart Disease Associated with Abnormal Connective Tissue Metabolism
Gerald S. Berenson, Associate Professor of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

Friday, June 10 (Continued)

Hemodynamic Determinants of Auscultatory Phenomenon in Pulmonic Stenosis with Open and Closed Septa
A. Calhoun Witham, Associate Professor of Medicine; Aleco Barrios, former Fellow in Cardiology; **Geoffrey E. King**, Instructor in Medicine, Medical College of Georgia, Augusta, Georgia

A New Device for Diagnosing Mediastinal Vascular Rings
Joseph W. Peabody, Jr., Instructor in Thoracic Surgery; Edgar W. Davis, Professor of Thoracic Surgery, Georgetown University School of Medicine, Washington, D. C.

Uncommon Causes for Continuous Murmurs
G. I. Shugoll, Lt., USN, MC, and Rufus J. Pearson, Jr., Captain, USN, MC, U. S. Naval Hospital, Bethesda, Maryland

Cine-cardiomediography in the Evaluation of Congenital Heart Disease (film)
F. Mason Sones, Jr., Director, Cardiac Catheterization Laboratory, Cleveland Clinic, Cleveland, Ohio

Clinical Use of Retrograde Left Ventricular Catheterization in Congenital Heart Disease
Edward W. Green, Associate Physician, Division of Pediatric Cardiology, Henry Ford Hospital; Doris Kavanagh-Gray, Fellow in Cardiology, St. Paul's Hospital, Vancouver, Canada; **Robert F. Ziegler**, Physician-in-Charge, Division of Pediatric Cardiology, Henry Ford Hospital, Detroit, Michigan

Left Atrial and Ventricular Volume in Coarctation of the Aorta
H. J. C. Swan, Mayo Clinic, Rochester, Minnesota; Ivan Bunnell, Assistant Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York; Donna Ikkos, Ulf Rudhe, Children's Clinic, Karolinska Sjukhuset, Stockholm, Sweden

Postoperative Vascular Complications of Coarctation of the Aorta
W. Glenn Young, Jr., Associate Professor of Surgery; Will C. Sealy, Professor of Thoracic Surgery; Jerome S. Harris, Professor of Pediatrics, Duke University Medical Center, Durham, North Carolina

Diagnosis and Surgical Correction of Triatrial Heart Type B
Conrad R. Lam, Surgeon-in-Charge, Division of Thoracic Surgery; Edward Green, Associate Physician, Division of Pediatric Cardiology; Eliet Drake, Senior Associate, Division of Cardiology, Henry Ford Hospital, Detroit, Michigan

Pericardial Disease Complicating Congenital Heart Lesions
Herbert J. Semler, Assistant to the Staff; Robert O. Brandenburg, Section of Medicine; John W. Kirklin, Section of Surgery, Mayo Clinic, Rochester, Minn.

12:00 noon — Round Table Discussions (See page 474)

2:00 p. m. — Scientific Session No. 1

Chairmen:
Edward H. Morgan, Seattle, Washington
Alfred Goldman, St. Louis, Missouri

Various Diseases of the Chest

Management of Symptomatic Hiatal Hernia and Associated Abnormalities with Balanced Operations
Jacob K. Berman, Associate Professor of Surgery; Edward J. Berman, Associate, Indiana University School of Medicine; Alban H. Lalonde, Staff, Methodist Hospital, Indianapolis, Indiana

Cervicomediastinal Cystic Hydroma
Richard A. Lim, Fellow in Surgery, Mayo Foundation; Matthew B. Divertie, Section of Medicine; Edgar G. Harrison, Jr., Section of Surgical Pathology; Philip E. Bernatz, Section of Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Carcinoma of the Lung: A Study of Five-year Survivals following Surgery
Eugene V. Kompaniez; Victor P. Satinsky, Mt. Sinai Hospital, Los Angeles, California.

Surgical Treatment of Primary Lymphoma of the Lung
Jacob Berghuis, Fellow; O. Theron Clagett, Section of Surgery; Edgar G. Harrison, Section of Surgical Pathology, Mayo Foundation, Rochester, Minnesota

Serum Protein Abnormalities in Neoplastic and Non-neoplastic Diseases of the Lung
Charles M. Carpenter, Professor of Infectious Diseases and Chairman of the Department; Charles L. Heiskell, Assistant Research Immunologist, Department of Infectious Diseases, University of California School of Medicine, Los Angeles, California

Alveolar Proteinosis: Further Observations
Samuel H. Rosen, Chief, Pulmonary, Mediastinal and ENT Pathology Branch, Armed Forces Institute of Pathology, Washington, D. C.

Differential Diagnosis of Surgical and Medical Bronchiectasis
John E. Rayl, Assistant Chief, Surgical Service; E. D. Peasley, Assistant Chief, Clinical Laboratory Service, Veterans Hospital, Oteen, North Carolina

The Facultative Pathogen in Serious Respiratory Infection
Roger H. L. Wilson, Assistant Clinical Professor of Medicine, University of California School of Medicine; J. Gerald Callanan, Attending Surgeon, San Francisco General Hospital, San Francisco, California

Friday, June 10 (Continued)

2:00 p. m. — Scientific Session No. 2

Chairmen:
M. Jay Flipse, Miami, Florida
John A. Lewis, London, Ontario

A Bipolar Electrode for Complete Heart Block

Samuel W. Hunter, Assistant Professor of Surgery, University of Minnesota; Norman A. Roth, St. Joseph's Hospital, St. Paul; Karel Absolon, University Hospital, Minneapolis, Minnesota

Transmural Ventricular Pressures in Experimental Cardiac Tamponade

Ralph Shabetai, Instructor in Medicine; Noble O. Fowler, Associate Professor of Medicine; John R. Braunstein, Assistant Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

The Physiological Advantage of Oxygen during Exercise in Patients with Pulmonary Emphysema and Coronary Insufficiency

Eduardo R. Pons, Jr., Instructor in Medicine; Judith L. Berg, Resident in Medicine, Columbia Research Division, Goldwater Memorial Hospital; Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City

Effects of Therapy on Lung Mechanics in Human Pulmonary Edema

John T. Sharp, Chief, Cardiopulmonary Laboratory, Veterans Hospital, Hines, Illinois; David G. Greene, Dent Professor of Clinical Research in Cardiovascular Disease; Ivan L. Bunnell, Assistant Professor of Medicine; Geraint T. Griffith, Associate in Medicine, University of Buffalo School of Medicine, Buffalo, New York

Effect of Cardiac Arrhythmias on the Circulation of the Vital Organs

Eliot Corday, Assistant Clinical Professor of Medicine, University of California School of Medicine; David W. Irving, Research Fellow, California Heart Association; Herbert Gold, Clinical Instructor of Medicine, University of California School of Medicine, Los Angeles, California

Effect of Myocardial Ischemia at Varying Temperatures on Left Ventricular Function and Tissue Oxygen Tension

J. J. Greenberg, Lt., MC, USNR, and L. H. Edmunds, Jr., Lt., MC, USNR, Department of Experimental Surgery, Naval Medical Research Institute, Bethesda, Maryland

Aldosterone Secretion and Arterial Hypertension

John H. Laragh, Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons; Stanley Ulick, Veterans Hospital (Bronx); Vlodzimierz Januszewicz, Warsaw, Poland; Quentin B. Deming, Goldwater Memorial Hospital; William G. Kelly and Seymour Lieberman, Associate Professor of Biochemistry, Columbia University College of Physicians and Surgeons, New York City

Low Incidence of Myocardial Infarction in Portal Cirrhosis of the Liver: A Review of 630 Cases of Liver Cirrhosis from 17,731 Autopsies

William L. Howell, Assistant Clinical Professor of Medicine, Georgetown University School of Medicine, Washington, D. C.

The Cardiopulmonary Response to Acute and Chronic Phlebotomy in Patients with Pulmonary Emphysema and Secondary Polycythemia

John F. Williams, Jr., American Heart Fellow; Douglas H. White, Instructor in Medicine; Roy H. Behnke, Associate Professor of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Role of Hypothermia in the Protection of Myocardial Metabolism during Cardiopulmonary By-pass and Elective Cardiac Arrest

Robert G. Ellison, Professor of Surgery; Sam A. Singal, Professor of Biochemistry; David P. Hall, Instructor in Surgery (Thoracic); Edwin L. Brackney, Associate Professor of Surgery; William H. Moretz, Professor and Chairman, Department of Surgery; Walter F. Butler, William C. Maloy and Joseph H. Rossi, Medical College of Georgia, Augusta, Georgia

8:15 p. m. — Scientific Session

FIRESIDE CONFERENCES

Subjects and Discussion Leaders

Interventricular Septal Defects

J. L. Ehrenhaft, Professor of Surgery and Chairman, Division of Thoracic Surgery, University of Iowa College of Medicine, Iowa City, Iowa
Joshua Lynfield, Research Associate, Pediatric Cardiology Department, Cook County Hospital, Chicago, Illinois

Management of Emphysema

James Kieran, Assistant Clinical Professor of Medicine, Stanford University School of Medicine, Oakland, California
Edward H. Morgan, Assistant Clinical Professor of Medicine, University of Washington School of Medicine, Seattle, Washington

Present Status of IPPB

Albert H. Andrews, Associate Clinical Professor of Bronchoesophagology, University of Illinois College of Medicine, Chicago, Illinois
William F. Miller, Associate Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Texas

Anticoagulant Therapy

Paul W. Boyles, Director, Coagulation Research Department, Miami Heart Institute, Miami Beach, Florida
E. Sterling Nichol, Associate Clinical Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Steroids in Pulmonary Disease

Hylan A. Bickerman, Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City
Ballard F. Smith, Chief of Medicine, Holy Cross Hospital, Fort Lauderdale, Florida

Electrocardiography in Children

Robert F. Ziegler, Physician-in-Charge, Division of Pediatric Cardiology, Henry Ford Hospital, Detroit, Michigan

Biopsy and Cytology in Diagnosis of Pulmonary Diseases

I. Alfred Breckler, Attending Staff, City of Hope Medical Center, Duarte, California
Seymour M. Farber, Chief, Tuberculosis and Chest Service, University of California, San Francisco General Hospital, San Francisco, California
Howard S. Van Ordstrand, Head, Department of Pulmonary Diseases, Cleveland Clinic, Cleveland, Ohio

Emotional Factors in Coronary Disease

Barney M. Dlin, Department of Psychiatry, Temple University Medical Center, Philadelphia, Pennsylvania
Henry I. Russek, Consultant in Cardiovascular Disease, U. S. Public Health Service Hospital, Staten Island, New York

The Staphylococcus Problem

N. Joel Ehrenkranz, Chief of Infectious Diseases, University of Miami School of Medicine, Miami, Florida
Joseph E. Geraci, Consultant in Medicine, Mayo Clinic, Rochester, Minnesota

Fibrinolysin Therapy in Cardiovascular Diseases

John S. LaDue, Associate Professor of Clinical Medicine, Cornell University Medical College, New York City
Kenneth M. Moser, Chief, Chest and Contagious Disease Clinic, National Naval Medical Center, Bethesda, Maryland
Paul Ruegsegger, Research Associate, Sloan-Kettering Institute, New York City

Fireside Conferences (Continued)

Congenital Tracheobronchial Malformations

Osler A. Abbott, Associate Professor of Surgery and Director, Division of Thoracic Surgery, Emory University School of Medicine, Atlanta, Georgia
Thomas G. Baffes, Attending Surgeon, Children's Memorial Hospital, Chicago, Illinois
Arthur DeBoer, Associate Attending Surgeon, Children's Memorial Hospital, Chicago, Illinois

Arrhythmias

Eliot Corday, Assistant Clinical Professor of Medicine, University of California School of Medicine, Los Angeles, California
Milton B. Hejtmancik, Associate Professor of Internal Medicine and Director, Heart Clinic, University of Texas Medical Branch, Galveston, Texas
Joseph K. Perloff, Director, Diagnostic Laboratory, Division of Cardiology, Georgetown University Hospital, Washington, D. C.

Oxygen Therapy in Heart Disease

Gustav J. Beck, Instructor in Medicine, Columbia University College of Physicians and Surgeons, New York City
Edwin R. Levine, Assistant Professor of Clinical Medicine, Chicago Medical School, Chicago, Illinois

Chemotherapy of Tuberculosis

Carl Muschenheim, Associate Professor of Clinical Medicine, Cornell University Medical College, New York City
Karl H. Pfuetze, Medical Director, Chicago State Tuberculosis Sanitarium, Chicago, Illinois

Mechanical Assists to the Circulation in Heart Failure

Joseph M. Hanner, Captain, MC, USN, Chief of Surgery, U. S. Naval Hospital, San Diego, California
Peter F. Salisbury, Consultant in Medicine and Head, Intensive Treatment Center, St. Joseph Hospital, Burbank, California

Occupational Diseases of the Lung

Henry J. Brock, Consultant on Dust Diseases, Workmen's Compensation Board, State of New York, Buffalo, New York
Peter A. Theodos, Assistant Professor of Clinical Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

Role of Adrenals in Hypertension

John H. Laragh, Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York City
Grace M. Roth, Consultant, Vascular Laboratory, Lovelace Clinic, Albuquerque, New Mexico
Albert Sjoerdsma, Chief, Section on Experimental Therapeutics, National Heart Institute, Bethesda, Maryland

Aerosol Therapy

Maurice S. Segal, Clinical Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts
Harry G. Smith, Chief, Division of Chest Diseases, City of Hope Medical Center, Duarte, California

Problems in Digitalis Therapy

Fred Wasserman, Chief, Medical Service, Veterans Hospital, Coral Gables, Florida
Henry A. Zimmerman, Chief, Cardiovascular Service, St. Vincent's Charity Hospital, Cleveland, Ohio

Surgery in Pulmonary Tuberculosis

J. Maxwell Chamberlain, Associate Clinical Professor of Surgery, Columbia University College of Physicians and Surgeons, New York City
Daniel A. Mulvihill, Associate Professor of Clinical Surgery, New York University, New York City

Problems in Cardiac Resuscitation

William B. Bunel, Chairman, Thoracic and Cardiovascular Division, Latter-Day Saints Hospital, Salt Lake City, Utah
Mark W. Wolcott, Associate Professor of Surgery, University of Miami School of Medicine, Miami, Florida

Clinical Pulmonary Physiology

Donald J. MacIntosh, Director, Cardiorespiratory Laboratory, Montreal General Hospital, Montreal, Canada
Joseph F. Tomashefski, Assistant Professor of Medicine and Physiology, Ohio State University College of Medicine, Columbus, Ohio

Fireside Conferences (Continued)

Problems in Diagnosis and Treatment of Coronary Insufficiency

Arthur M. Master, Consultant Cardiologist, Mt. Sinai Hospital, New York City
Isadore Rosenfeld, Instructor in Medicine, Cornell University Medical College, New York City

Atypical Coronary Disease

William Likoff, Director, Cardiovascular Section, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
Myron Prinzmetal, Professor of Clinical Medicine, University of California School of Medicine, Los Angeles, California
Raymond Scalettar, Captain, MC, USA, Chief, General Medicine Section 3, Walter Reed General Hospital, Washington, D. C.

The Solitary Nodule

Oscar H. Friedman, Associate Physician for Chest Diseases, Mt. Sinai Hospital, New York City
Elmer C. Rigby, Staff Thoracic Surgeon, St. Vincent's Hospital, Los Angeles, California
John W. Vance, Assistant in Medicine, Millard Fillmore Hospital, Buffalo, New York

Problem of Atypical Acid-Fast Bacilli

James O. Bond, Director, Bureau of Preventable Diseases, State Board of Health, Jacksonville, Florida
E. Charlton Prather, Florida State Board of Health, Jacksonville, Florida
Guy P. Youmans, Professor and Chairman, Department of Microbiology, Northwestern University Medical School, Chicago, Illinois

Fungus Infections

Michael L. Furcolow, Medical Director, U. S. Public Health Service, Communicable Disease Center, University of Kansas School of Medicine, Kansas City, Kansas
John P. Utz, Chief, Infectious Disease Service, Clinical Center, National Institutes of Health, Bethesda, Maryland

Surgery of Lung Tumors

Alfred Goldman, Chief of Thoracic Surgery, Cedars of Lebanon Hospital, City of Hope Medical Center, Beverly Hills, California
Robert B. White, Clinical Instructor in Surgery, University of Illinois College of Medicine, Aurora, Illinois

Allergy in Pulmonary Disease

Edward Egbert, Staff, El Paso General Hospital, El Paso, Texas
George R. Piness, Associate Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California

Newer Endoscopic Techniques

Andre Mackay, Director, Chest Clinic, Notre-Dame Hospital, Montreal, Canada
Henry J. Stanford, Consultant Thoracic Surgeon, Veterans Hospital, Tucson, Arizona

Home Treatment of Tuberculosis

Ezra V. Bridge, Chief of Medicine, Port Huron Hospital, Port Huron, Michigan
Earl T. Opstad, Instructor, University of Minnesota Hospitals, Minneapolis, Minnesota

NOTE

These conferences are informal and offer an opportunity for free discussion of many subjects of interest to our members. Discussion Leaders will be seated at tables with proper identification. Physicians may participate in the discussion of their choice, or move on to other discussions when and if they desire. Refreshments will be available by courtesy of the technical exhibitors.

Saturday, June 11

9:00 a.m. — Scientific Session No. 1

Chairmen:

Donato G. Alarcon, Mexico City, Mexico

Coleman B. Rabin, New York, New York

TUBERCULOSIS AND OTHER PULMONARY GRANULOMAS

The Immunogenicity of Fractions Obtained from Mycobacteria

Guy P. Youmans, Professor and Chairman, Department of Microbiology, Northwestern University Medical School, Chicago, Illinois

Effect of Direct Irradiation of the Lung on the Course of Pulmonary Tuberculosis (Using Cancericidal Doses)

I. D. Bobrowitz, Associate Clinical Professor of Medicine (Pulmonary Diseases); Milton Elkins, Professor of Radiology; John C. Evans, Associate Professor of Radiology; Albert Lin, Instructor in Radiology, Albert Einstein College of Medicine, New York City

Choice of Initial Treatment Regimen in Pulmonary Tuberculosis

Alex Saliba, Staff Physician; Oren A. Beatty, Medical Director, District Two State Tuberculosis Hospital, Louisville, Kentucky

Pulmonary Resection in the Treatment of Tuberculosis

John H. Foster, Assistant Professor of Surgery; Duncan A. Killen, Instructor in Surgery; Walter L. Diveley, Assistant Clinical Professor of Surgery, Vanderbilt University School of Medicine; Robert L. McCracken, Chief, Surgical Service; Walton W. Hubbard, Medical Director, Middle Tennessee Tuberculosis Hospital, Nashville, Tennessee

Effect of Psychologic Adjustment on the Success of Tuberculosis Chemotherapy

Claire M. Vernier, Director, Central Laboratory Cooperative Psychological Research, Veterans Hospital, Baltimore, Maryland

Sulfonamide Tuberculostatis

William Weiss, Clinical Assistant Professor of Medicine, Woman's Medical College; George M. Eisenberg, Assistant Professor of Clinical Microbiology (deceased); Harrison F. Flippin, Professor of Clinical Microbiology, The Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Fever Curve as an Indicator for Steroid Therapy in Miliary Tuberculosis

Jerome A. Gold, Assistant Attending Physician, Pulmonary Disease Service, Kings County Medical Center, Brooklyn, New York

Rehabilitation of Chronic, Drug Resistant Cases of Tuberculosis with Cycloserine, and Successful Treatment of Virgin Cases

Israel G. Epstein, Associate Professor of Medicine; K. G. S. Nair, Michael G. Mulinos, Emanuel Horiuchi, and Benjamin Encarnacion, New York Medical College, Metropolitan Medical Center and Commercial Solvents Corporation, New York City

Epidemiology of Infection Due to Atypical Acid-Fast Bacilli; Preliminary Report

E. Charlton Prather, James O. Bond, Eldert C. Hartwig, Florida State Board of Health; F. P. Dunbar, Southwest Florida Tuberculosis Hospital, Jacksonville, Florida

Newton County Pilot Study: A County-wide School Certification Program for Tuberculosis Control (Using the Mantoux Tuberculin Test as a Diagnostic Screening Agent)

Charles A. Brasher, Medical Director, Missouri State Sanatorium, Mt. Vernon, Missouri

Saturday, June 11 (continued)

9:00 a.m. — Scientific Session No. 2

Chairmen:

Eliot Corday, Los Angeles, California
Donald R. McKay, Buffalo, New York

Straight Back Syndrome: A New Heart Disease

Maurice S. Rawlings, Visiting Physician, Memorial and Baroness Erlanger Hospitals, Chattanooga, Tennessee

Effect of Digitalis in Patients with Cardiomegaly without Congestive Cardiac Failure

Henry A. Zimmerman, Chief, Cardiovascular Service, St. Vincent's Charity Hospital, Cleveland, Ohio

Pericardial Effusion in Congestive Heart Failure: Incidence and Significance

Louis A. Soloff, Professor of Clinical Medicine; William L. Winters, Jr., Instructor in Medicine; Barbara L. Carter, Instructor in Radiology; Herbert M. Stauffer, Professor of Radiology, Temple University School of Medicine, Philadelphia, Pennsylvania

Mitral Regurgitation following Mitral Commissurotomy

Joseph F. Uricchio, Assistant Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

10:05 a.m. — Symposium on Myocardial Diseases

Moderator:

George E. Burch, Henderson Professor and Chairman, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana

Etiological and Pathological Features of Myocarditis

William C. Manion, Chief, Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, D. C.

Chronic "Non-specific" Myocarditis—A Forgotten Clinical Entity

Earl N. Silber, Research Associate, Cardiovascular Department, Michael Reese Hospital and Medical Center, Chicago, Illinois

Idiopathic Myocardial Hypertrophy

Marvin A. Sackner, Resident in Medicine; David H. Lewis, Chief, Hemodynamics Section; Morton J. Robinson, Resident in Pathology; Samuel Bellet, Director, Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania

Evaluation of Auscultatory Findings in Myocardial Disease

W. Proctor Harvey, Associate Professor of Medicine and Director, Division of Cardiology; **Joseph K. Perloff,** Instructor in Medicine and Director, Cardiac Diagnostic Laboratory, Georgetown University Hospital, Washington, D. C.

Muscle Biopsies in the Diagnosis of Myocarditis

Don C. Sutton, Professor of Medicine Emeritus; George C. Sutton, Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Illinois

Prolonged Bed Rest in the Treatment of Myocarditis

John J. Walsh, Research Laboratory, U. S. Public Health Service Hospital; George E. Burch, Henderson Professor and Chairman, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana

Questions from floor

Summary by moderator

Saturday, June 11 (continued)

12:00 noon — Round Table Discussions (See page 475)

2:00 p. m. — Scientific Session No. 1

Chairmen:

Andrew L. Banyai, Chicago, Illinois
Alexander Libow, Miami Beach, Florida

PULMONARY GRANULOMAS (CONTINUED)

Pulmonary Sarcoidosis: Diagnosis and Treatment

H. W. Gierson, Assistant Clinical Professor of Thoracic Diseases, College of Medical Evangelists, Los Angeles, California

The Use of Fluorescent Antibody in the Diagnosis of Mycotic Infections of the Lung

Harold J. Lynch, Jr., Senior Assistant Surgeon (R), Communicable Disease Center, U. S. Public Health Service, Kansas City Field Station, Kansas City, Kansas

Therapy of 100 Cases of Histoplasmosis with Amphotericin B

Michael L. Furcolow, Medical Director, Chief, Kansas City Field Station, Public Health Service, Communicable Disease Center, Bureau of State Service, U. S. Department of Health, Education and Welfare, Kansas City, Kansas

DIAGNOSTIC PANEL

Moderator:

John P. Medelman, Associate Professor of Radiology, University of Minnesota Medical School, St. Paul, Minnesota

Panel:

F. E. Donoghue, Mayo Clinic, Rochester, Minnesota
Roy R. Greening, Department of Radiology, Jefferson Medical College Hospital, Philadelphia, Pennsylvania
David H. Waterman, Senior Attending Thoracic Surgeon, University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee

2:00 p. m. — Scientific Session No. 2

Chairmen:

Stephen R. Elek, Los Angeles, California
George R. Herrmann, Galveston, Texas

Emotional Stress and Coronary Heart Disease in Physicians

Henry I. Russek, Consultant in Cardiovascular Disease, U. S. Public Health Service Hospital, Staten Island, New York

Considerations in the Treatment of Hypercholesteremia

William Likoff, Director, Cardiovascular Section, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

2:30 p.m. — Symposium on Electrocardiography in Chest Diseases

The Master "Two-Step" Exercise Electrocardiogram: Recent Developments

Arthur M. Master, Consultant Cardiologist, Mt. Sinai Hospital; Isadore Rosenfeld, Instructor in Medicine, Cornell University Medical College; Ephraim Donoso, Assistant in Cardiology, Mt. Sinai Hospital, New York City

The Ventricular Gradient: Experimental Verification of the Concept of Its Theoretic and Practical Applications

Manuel Gardberg, Clinical Professor of Medicine; Irving L. Rosen, Instructor in Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

Chemical Origin of ST Elevation and Depression in Non-Ischemic Cardiac Conditions

Myron Prinzmetal, Clinical Professor of Medicine; Ali Ekmekci, Research Fellow, Los Angeles County Heart Association; Hideo Toyoshima, Advanced Research Fellow, American Heart Association; Jan Kwoczynski, Research Fellow, The Rockefeller Foundation, University of California School of Medicine, Los Angeles, California

ECG Changes after Cardiac Surgery

Harry Goldberg, Assistant Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

Sunday, June 12

9:00 a.m. — Scientific Session No. 1

Chairmen:
Carl C. Aven, Atlanta, Georgia
Alfred Goldman, Beverly Hills, California

EMPHYSEMA AND RELATED DISEASES

Four and One Half Years' Experience in the Treatment of Emphysema and other Respiratory Insufficiencies by Tracheal Fenestration

E. E. Rockey, Clinical Instructor in Surgery; Samuel A. Thompson, Associate Professor of Surgery, New York Medical College-Metropolitan Medical Center; Charles F. Blazsik, St. Anthony's Hospital (Woodhaven), New York City

Tracheal Fenestration: A Critical Evaluation

Mark W. Wolcott, Associate Professor of Surgery, University of Miami School of Medicine; **Thomas J. Kiernan,** Resident in Surgery, Veterans Hospital, Coral Gables; George L. Baum, Assistant Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Surgical Approach to Pulmonary Emphysema

Otto C. Brantigan, Chief Surgeon, Church Home and Hospital; Milton B. Kress, Instructor in Medicine, Johns Hopkins University School of Medicine, and Eugene Mueller, Baltimore, Maryland

Experience with Newer Methods of Reconstruction of Congenital Chest Wall Defects

Osler A. Abbott, Associate Professor of Surgery and Chairman, Division of Thoracic Surgery; Joseph H. Patterson, Associate Professor of Pediatrics; Richard W. Blumberg, Chairman and Professor of Pediatrics, Emory University School of Medicine, Atlanta, Georgia

Cystic Fibrosis and Its Relation to Chronic Lung Disease in Children

Paul E. A. di Sant'Agnese, Clinical Professor of Pediatrics, Georgetown University School of Medicine, Washington, D. C.

Pulmonary Diffusing Capacity in Patients with Emphysema: Correlation with Severity of Disease

George N. Bedell, Associate Professor of Medicine; Richard W. Adams, Junior Medical Student, University of Iowa School of Medicine, Iowa City, Iowa

Methods of Differentiating Pulmonary from Cardiovascular Causes of Pulmonary Hypertension

John Rankin, Associate Professor of Medicine, Cardiopulmonary Laboratory, University of Wisconsin Medical School, Madison, Wisconsin

The Association of Chronic Peptic Ulcer and Chronic Pulmonary Emphysema

John H. Kathe, Staff Physician; George L. Baum, Chief, Non-tuberculous Pulmonary Disease Section; Martin Kalser, Chief, Gastro-enterology Section, Veterans Hospital, Coral Gables, Florida

Treatment of Advanced Pulmonary Insufficiency in Pulmonary Emphysema

Richard T. Cathcart, Assistant Professor of Medicine; William Fraimow, Instructor in Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

9:00 a.m. — Scientific Session No. 2

Chairmen:
Alvis E. Greer, Houston, Texas
H. Easton McMahon, New York, New York

SYMPOSIUM ON PROBLEMS IN DIAGNOSIS AND MANAGEMENT OF CORONARY DISEASE

Moderator:
John F. Briggs, Associate Professor of Clinical Medicine, University of Minnesota Medical School, St. Paul, Minnesota

Introductory Remarks

John F. Briggs

The Incidence and Significance of Chest Pain in a Comparable Group of Doctors, Lawyers and Farmers

Charles H. Schiefley and John J. Whitaker, Mayo Clinic, Rochester, Minnesota

Trace Metals in Myocardial Infarction

George C. Griffith, Professor of Medicine; Balakrishna Hegde, Research Fellow; Edward M. Butt, Professor of Pathology, University of Southern California School of Medicine, Los Angeles, California

Sunday, June 12 (continued)

Impending Myocardial Infarction: Diagnostic Features and Therapy

E. Sterling Nichol, Associate Clinical Professor of Medicine, University of Miami School of Medicine, Miami, Florida

Psychology of Delayed Recovery in Coronary Thrombosis

Edward W. Weiss, Department of Medicine (deceased); **Barney M. Dlin,** H. K. Fischer, S. Hagner, G. W. Russell, Department of Psychiatry; William L. Winters, Jr., Department of Medicine, Temple University Medical Center, Philadelphia, Pennsylvania

Cine Coronary Arteriography (film)

F. Mason Sones, Jr., Director, Cardiac Catheterization Laboratory, Cleveland Clinic, Cleveland, Ohio

PANEL DISCUSSION

Participants in morning program

Additional Panel members:

Surgical Treatment of Complications of Myocardial Infarction

Charles P. Bailey, Chairman and Professor of Surgery, New York Medical College, Flower & Fifth Avenue Hospital, New York City

Surgical Aspects of the Treatment of Coronary Heart Disease

F. Henry Ellis, Jr., Head of a Surgical Section, Mayo Clinic; Assistant Professor of Surgery, Mayo Foundation Graduate School of the University of Minnesota, Rochester, Minnesota

Present Status of Fibrinolysin in the Treatment of Coronary Disease

Kenneth M. Moser, Chief, Chest and Contagious Disease Clinic, Bethesda Naval Hospital, Bethesda, Maryland

CARDIAC REHABILITATION

Rehabilitation of the Coronary Thrombosis Patient

Rudolph T. Wagner, Senior Physician, Mt. Sinai Hospital, Miami Beach, Florida

Broad Spectrum Cardiovascular Rehabilitation

Harold Bernstein, Assistant Visiting Physician, Peripheral Vascular Service, Queens Hospital Center, (Jamaica), Rockville Centre, New York

12:00 noon — Round Table Luncheon Discussions (See page 476)

2:00 p.m. — Combined Scientific Session

Chairmen:
Hollis E. Johnson, Nashville, Tennessee
Ray W. Kissane, Columbus, Ohio

SYMPOSIUM ON CHEST TRAUMA

Moderators:
Thomas W. Mattingly, Washington, D. C.
R. Drew Miller, Rochester, Minnesota

Opening Remarks by Moderators

Pathology of Chest Trauma

William C. Manion, Chief, Cardiovascular Surgery, Armed Forces Institute of Pathology, Washington, D. C.

Management of Acute Trauma

Dwight E. Harken, Associate Professor of Clinical Surgery, Harvard Medical School, Boston, Massachusetts
Emil A. Naclerio, Chief, Thoracic Surgical Services, Harlem and Columbus Hospitals, New York City

Problem in Recognition and Management of Complications and Sequelle

Paul H. Holinger, Professor of Bronchoesophagology, University of Illinois College of Medicine, Chicago, Illinois
Loren F. Parmley, Lt. Colonel, MC, USA, Chief, Cardiology Service, Letterman Army Hospital, San Francisco, California

Surgical Management of Complications and Sequelle

Charles A. Hufnagel, Associate Professor of Surgery, Professor of Surgical Research, Georgetown University Medical Center, Washington, D. C.
Donald L. Paulson, Clinical Associate Professor of Thoracic Surgery, University of Texas Southwestern Medical School, Dallas, Texas

Discussion by members and questions from the floor

Summary by moderators

2:30 p.m.—*Open Forum sponsored by the Committee on Tuberculosis*

TUBERCULOSIS: Case-Finding — Control — Eradication

Chairman:

Irving Willner, Director, Division of Chest Diseases, Department of Health, Newark, New Jersey

Bovine Tuberculosis Eradication

A. F. Ranney, Chief Staff Officer, Tuberculosis Eradication, Agricultural Research Service, Animal Disease Eradication Division, U. S. Department of Agriculture, Washington, D. C.

Prompt Treatment in Tuberculosis Control; The Experience of Puerto Rico

J. Rodriguez Pastor, Medical Director, Antillas Clinic Medical Staff, Rio Piedras, Puerto Rico

"Tuberculin Sensitivity and Tuberculosis in Medical Students"

James R. Karns, Associate Professor of Medicine, In Charge of Student Health, University of Maryland School of Medicine, Baltimore, Maryland

Panel Discussion

Moderator:

Lewis S. Jordan, Superintendent, Riverside Sanatorium, Granite Falls, Minnesota, Chairman, Committee on Tuberculosis, American College of Chest Physicians

Panel:

Arnold S. Anderson, St. Anthony and Mound Park Hospitals, St. Petersburg, Florida

Charles A. Brasher, Superintendent and Medical Director, Missouri State Sanatorium, Mt. Vernon, Missouri

H. M. Hardwicke, Deputy Health Officer, State of Missouri, Jefferson City, Missouri

J. Arthur Myers, Professor (Emeritus) of Internal Medicine and Public Health, University of Minnesota Medical and Graduate Schools, Minneapolis, Minnesota

H. Allan Novack, Tuberculosis Division, Health Department of Boston, Boston, Massachusetts

William A. Smith, State Board of Health, Raleigh, North Carolina

Henry C. Sweany, Director of Research, Missouri State Sanatorium, Mt. Vernon, Missouri

Questions and answers from the floor

2:30 p.m. — *Open Forum sponsored by the Council and Committee on Undergraduate Medical Education*

UNDERGRADUATE TEACHING OF CHEST DISEASES

The Council and Committee on Undergraduate Medical Education have selected the teaching programs in several medical schools, as they relate to diseases of the chest, which will be presented by members of the College affiliated with those schools. A special point of interest will be the discussion of the use of the pulmonary function laboratory as an instrument of teaching chest disease.

Moderator:

Theodore H. Noehren, Assistant Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York

Panel:

William F. Miller, Associate Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Texas

John A. Prior, Chief, Division of Pulmonary Diseases, The Ohio State University Health Center, University Hospital, Columbus, Ohio

Donald L. Paulson, Clinical Associate Professor of Surgery, University of Texas Southwestern Medical School, Dallas, Texas

The panel has been chosen to initiate the discussion and all members of the College who are engaged in teaching programs are encouraged to attend this session and join a general discussion of these problems.

All Physicians Are Invited to Attend

ROUND TABLE LUNCHEONS

Friday, June 10

A-1 ***Management of the Cyanotic Newborn***

Thomas G. Baffes, Attending Surgeon, Children's Memorial Hospital, Chicago, Illinois

Alvin A. Bakst, Director, Cardiovascular and Thoracic Surgery, Jewish Hospital, of Brooklyn, Brooklyn, New York

Oscar Creech, Jr., Professor of Surgery, Tulane University School of Medicine, New Orleans, Louisiana

Donald B. Effler, Chief, Department of Thoracic Surgery, Cleveland Clinic, Cleveland, Ohio

Wilford B. Neptune, Associate, Overholt Thoracic Clinic, Boston, Massachusetts

Moderator: **Charles P. Bailey,** Chairman and Professor of Surgery, New York Medical College, Flower & Fifth Avenue Hospitals, New York City

A-2 ***Pulmonary Hypertension***

J. L. Ehrenhaft, Professor of Surgery and Chairman, Division of Thoracic Surgery, University of Iowa College of Medicine, Iowa City, Iowa

Maurice Lev, Director, Congenital Heart Disease Research and Training Center, Hektoen Institute, Chicago, Illinois

H. J. C. Swan, Assistant Professor of Physiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Robert F. Ziegler, Physician-in-Charge, Division of Pediatric Cardiology, Henry Ford Hospital, Detroit, Michigan

Moderator: **Donald E. Cassels,** Professor, Department of Pediatrics, University of Chicago Clinics, Chicago, Illinois

A-3 ***Chemotherapy of Tuberculosis***

Albert R. Allen, Selah, Washington

W. Leonard Howard, Superintendent, William H. Maybury Sanatorium, Northville, Michigan

George E. Martin, Medical Director, C. Howard Marcy State Hospital, Pittsburgh, Pennsylvania

Moderator: **Sumner Cohen,** Clinical Assistant Professor of Medicine, University of Minnesota Medical School, Oak Terrace, Minnesota

A-4 ***Treatment of the Patient with Unresectable Lung Cancer***

Robert E. Lee, Consultant in Therapeutic Radiology, Mayo Clinic, Rochester, Minnesota

Richard H. Overholt, Director, Overholt Thoracic Clinic, Boston, Massachusetts

Forrest M. Willett, Chairman, Western Cooperative Cancer Chemotherapy Group, Fort Miley Veterans Hospital, San Francisco, California

Moderator: **Donald R. McKay,** Associate Clinical Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York

A-5 ***Indications for Abbreviated Preoperative Tuberculosis Chemotherapy***

J. Maxwell Chamberlain, Associate Clinical Professor of Surgery, Columbia University College of Physicians and Surgeons, New York City

Carl Muschenheim, Associate Professor of Clinical Medicine, Cornell University Medical College, New York City

Karl H. Pfuetze, Medical Director and Superintendent, Chicago State Tuberculosis Sanitarium, Chicago, Illinois

Moderator: **Norman J. Wilson,** Thoracic Surgeon, New England Deaconess Hospital, Boston, Massachusetts

A-6 ***Sarcoidosis***

Robert L. Mayock, Associate Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Arthur M. Olsen, Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota

Louis E. Siltzbach, Associate Physician, Department of Medicine, Mt. Sinai Hospital, New York City

Moderator: **Edward Dunner,** Associate Director and Chief, Cooperative Studies Division, Research Service, Veterans Administration Central Office, Washington, D. C.

ROUND TABLE LUNCHEONS

Saturday, June 11

R-1 *Use of Monoamine Oxidase Inhibitors in Cardiovascular Diseases*

Seymour L. Cole, Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Beverly Hills, California

Arthur M. Master, Consultant Cardiologist, Mt. Sinai Hospital, New York City

Albert T. Sjoerdsma, Chief, Section on Experimental Therapeutics, National Heart Institute, Bethesda, Maryland

Gerhard Zbinden, Director of Biological Research, Hoffman-LaRoche, Inc., Nutley, New Jersey

Moderator: **George C. Griffith,** Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California

R-2 *Pumps and Circulatory Assists*

Robert S. Cartwright, Chief, Section of Cardiovascular Surgery and Head, Department of Surgical Research, Lovelace Clinic and Foundation, Albuquerque, New Mexico

Wilford B. Neptune, Associate, Overholt Thoracic Clinic, Boston, Massachusetts

Gerald H. Pratt, Associate Clinical Professor of Surgery, New York University College of Medicine and Attending Surgeon in Charge, Cardiovascular Surgery, St. Vincent's Hospital, New York City

Warren J. Taylor, Associate Surgeon, Peter Bent Brigham Hospital, Boston, Massachusetts

Moderator: **Donald B. Effler,** Chief, Department of Thoracic Surgery, Cleveland Clinic, Cleveland, Ohio

R-3 *Etiologic Evaluation of Pulmonary Fibrosis*

Lawrence McCormack, Pathologist, Cleveland Clinic, Cleveland, Ohio

Coleman B. Rabin, Attending Physician for Chest Diseases and Associate Radiologist, Mt. Sinai Hospital, New York City

Maurice S. Segal, Clinical Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts

Moderator: **Howard S. Van Ordstrand,** Head, Department of Pulmonary Diseases, Cleveland Clinic, Cleveland, Ohio

R-4 *Early Diagnosis of Pulmonary Emphysema*

George N. Bedell, Associate Professor of Medicine, University of Iowa School of Medicine, Iowa City, Iowa

Roy F. Goddard, Director, Department of Pediatric Research, Lovelace Foundation, Albuquerque, New Mexico

Edwin R. Levine, Assistant Professor of Clinical Medicine, Chicago Medical School, Chicago, Illinois

Moderator: **Hurley L. Motley,** Professor of Medicine and Director, Cardiorespiratory Laboratory, University of Southern California School of Medicine, Los Angeles, California

R-5 *Air Pollution and Carcinogenesis*

Henry J. Brock, Consultant on Dust Diseases, Workmen's Compensation Board, State of New York, Buffalo, New York

L. P. Herrington, Department of Public Health, Yale University School of Medicine, New Haven, Connecticut

Peter A. Theodos, Assistant Professor of Clinical Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

Moderator: **Seymour M. Farber,** Chief, Tuberculosis and Chest Service, University of California, San Francisco General Hospital, San Francisco, California

R-6 *Surgical Treatment of Carcinoma of the Lung: Indications for Conservative Resection*

David P. Boyd, Division of Thoracic Surgery, Lahey Clinic, Boston, Massachusetts

John B. Grow, Chief of Thoracic Surgery, National Jewish Hospital, Denver, Colorado

Irving Sarot, Associate Clinical Professor of Thoracic Surgery, New York Polyclinic Medical School and Hospital, New York City

Moderator: **Philip Bernatz,** Mayo Clinic, Rochester, Minnesota

ROUND TABLE LUNCHEONS

Sunday, June 12

C-1 ***New Horizons in Valve Surgery***

Charles A. Hufnagel, Professor of Surgery, Georgetown University Medical School, Washington, D. C.

Earle B. Kay, Chief, Cardiovascular and Thoracic Surgery and Director, Cardiovascular Research, St. Vincent Charity Hospital, Cleveland, Ohio

Robert S. Litwak, Chief, Division of Thoracic and Cardiovascular Surgery, University of Miami School of Medicine, Miami, Florida

Moderator: **Dwight E. Harken,** Associate Clinical Professor of Surgery, Harvard Medical School, Boston, Massachusetts

C-2 ***After the Acute Cardiac Episode—What?***

Harold Bernstein, Assistant Visiting Physician, Peripheral Vascular Service, Queens Hospital Center (Jamaica), Rockville Centre, New York

Irvin Klein, Medical Director, Workmen's Compensation Board, State of New York, New York City

Edward A. Reilly, Cardiologist, St. John's Episcopal Hospital, Brooklyn, New York

Rudolph T. Wagner, Senior Physician, Mt. Sinai Hospital, Miami, Florida

Co-moderators: **H. Easton McMahon,** Assistant Clinical Professor of Medicine (Cardiology), New York Medical College, New York City
Nathaniel E. Reich, Assistant Clinical Professor of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York

C-3 ***Newer Simple Methods for Pulmonary Function Testing***

Ross C. Kory, Director, Cardiopulmonary Laboratory, Wood Veterans Hospital, Milwaukee, Wisconsin

John Rankin, Associate Professor of Medicine, Cardiopulmonary Laboratory, University of Wisconsin Medical School, Madison, Wisconsin

Robert B. Stonehill, Lt. Colonel, USAF, MC, Chief, Pulmonary Disease Services, USAF Hospital, Lackland AFB, Texas

Moderator: **Roger H. L. Wilson,** Assistant Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

C-4 ***Open Negative Cases: Resect or Not Resect***

George A. Cunningham, Active Staff, St. Mary's and Good Samaritan Hospitals, West Palm Beach, Florida

Daniel E. Smith, Assistant Chief, Thoracic Surgical Section, Veterans Hospital, Oteen, North Carolina

James A. Wier, Colonel, USA, MC, Chief, Pulmonary Disease Service, Fitzsimons General Hospital, Denver, Colorado

Moderator: **Oscar Auerbach,** Senior Medical Investigator, Veterans Hospital, East Orange, New Jersey

C-5 ***Newer Antibiotics and Resistant Pathogens in Pulmonary Disease***

Charles M. Carpenter, Professor of Infectious Diseases and Chairman of the Department, University of California School of Medicine, Los Angeles, California

N. Joel Ehrenkranz, Chief of Infectious Diseases, University of Miami School of Medicine, Miami, Florida

Ellard M. Yow, Professor of Medicine, Baylor University College of Medicine, Houston, Texas

Moderator: **Alexander Libow,** Associate Attending, Mt. Sinai Hospital, Miami Beach, Florida

C-6 ***Allergy as a Factor in Emphysema***

J. S. Blumenthal, Associate Clinical Professor of Medicine and Director of Allergy Clinics, University of Minnesota Medical School, St. Paul, Minnesota

Lloyd D. Mayer, Staff, St. Joseph, Good Samaritan, Central Baptist Hospitals, Lexington, Kentucky

Donald L. Unger, Clinical Assistant in Medicine (Allergy), Stritch Medical School of Loyola University, Chicago, Illinois

Moderator: **Clarence S. Thomas,** Clinical Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

ADMINISTRATIVE SESSIONS

Wednesday June 8

8:30 a. m. — Committee on Postgraduate Seminars
10:00 a. m. — Executive Council Meeting
2:00 p. m. — Board of Regents Meeting
2:00 p. m. — Committee on Scientific Program
4:00 p. m. — Committee on Nominations
4:00 p. m. — Committee on Bylaws

The Technical Exhibits will open at 9:00 a.m.

Thursday, June 9

8:00 a. m. — Breakfast Meetings
Council on Cardiovascular Research
Council on Pulmonary Research

9:00 a. m. — Meetings of all Councils and Committees
9:00 a. m. — Examinations for Fellowship (written)
12:00 noon — **LUNCHEON, JOINT MEETING**

Board of Governors and Board of Regents
Howell S. Randolph, Phoenix, Arizona, Chairman,
Board of Governors, presiding

Awarding of Certificates of Merit to Past-Presidents of College Chapters
Seymour M. Farber, San Francisco, California, President

Presentation of Council and Committee Reports

1:30 p. m. — Meeting, Oral Examiners
2:00 p. m. — Examinations for Fellowship (oral)
2:00 p. m. — **OPEN ADMINISTRATION SESSION**
Seymour M. Farber, San Francisco, California, President, presiding
Report of the Historian
Carl C. Aven, Atlanta, Georgia
Report of the Treasurer
Charles K. Petter, Waukegan, Illinois
Report of the Executive Director
Murray Kornfeld, Chicago, Illinois
Report of the Committee on Nominations
Burgess L. Gordon, Albuquerque, New Mexico
Election of Officers

3:30 p. m. — **Joint Meeting,** Members of the National and State Committees on Membership, College Chapter Officials, and members of the Committee on Liaison with State and County Medical Societies
William E. Adams, Chicago, Illinois, Chairman, Illinois State Committee on Membership, American College of Chest Physicians, presiding
Guest Speaker: **Herman J. Moersch,** Director, Medical Education and Research, American College of Chest Physicians

Friday, June 10

2:00 p. m. — Committee on Insurance
3:00 p. m. — Editorial Board, **Diseases of the Chest**
5:00 p. m. — Board of Examiners
5:00 p. m. — Chapter Meetings

Saturday, June 11

6:00 p. m. — Convocation
7:00 p. m. — Cocktail Party
(sponsored by the Florida Chapter of the College)
7:30 p. m. — **ANNUAL PRESIDENT'S BANQUET**
An evening for fun — no speeches — after-dinner dancing

Sunday, June 12

8:00 a. m. — Past Presidents' Breakfast
10:00 a. m. — Executive Council Meeting
2:30 p. m. — Board of Regents Meeting

MOTION PICTURE PROGRAM

The following is a tentative program of films which will be shown concurrently with the scientific program on Friday, Saturday and Sunday, June 10, 11 and 12.

Radiation: Physician and Patient
By the American College of Radiology in cooperation with the U. S. Public Health Service, supported by a grant from The Rockefeller Foundation.

Fusiform Aneurysm of Aortic Arch, Resection and Replacement with Dacron Graft
Michael E. DeBakey and George C. Morris, Jr., Baylor University College of Medicine, Houston, Texas

Endobronchial and Endoesophageal Views
J. M. DuBois de Montreynaud and S. Segal, Anti-Cancer Centre, Rheims, France

That They May Live — Direct Artificial Respiration
Allen B. Dobkin and M. H. Brook, University of Saskatchewan College of Medicine, Saskatoon, Canada

Segmental Resection of an Arteriovenous Fistula of the Lung
J. L. Ehrenhaft and Montague S. Lawrence, State University of Iowa Hospitals, Iowa City, Iowa

Emergency Thoracic Surgery in the Newborn
J. L. Ehrenhaft and Montague S. Lawrence, State University of Iowa Hospitals, Iowa City, Iowa

Esophageal Hiatal Hernia, Sliding Type
Leo C. Harris and Arthur A. Calix, District No. 1, Tuberculosis Sanatorium, Decatur, Alabama

Cavernostomy
Chuzo Nagaishi, Tuberculosis Research Institute, Kyoto University, Kyoto, Japan

Direct Intracavitary Insufflation with Chemotherapeutic Agent Using Metra's Catheter Via Tracheo-Bronchial Route
Chuzo Nagaishi, Tuberculosis Research Institute, Kyoto University, Kyoto, Japan

Intermittent Positive Pressure Breathing (IPPB/I), Its Clinical Application and Administration
Theodore H. Noehren, Buffalo General Hospital, University of Buffalo, Buffalo, New York

Achalasia of the Esophagus: Diagnosis and Treatment
Arthur M. Olsen and F. Henry Ellis, Jr., Mayo Clinic, Rochester, Minnesota

The Clinical Course and Surgical Technic of Tracheal Fenestration
E. E. Rockey, Samuel A. Thompson and C. F. Blazsik, New York Medical College, Metropolitan Medical Center, New York City; St. Anthony's Hospital, Woodhaven, New York

Surgical Anatomy of the Pulmonary Hilum
Franklin R. Smith and Edward A. Boyden, University of Washington, Seattle, Washington

Air Travel and the Cardiopulmonary Patient
Robert B. Stonehill, Lt. Col., MC, USAF, United States Air Force, Technical Advisor

LADIES ACTIVITIES

Ladies attending the meeting are invited to register and receive guest badges. Tickets for the ladies functions are limited and may be ordered in advance.

Friday, June 10

6:00 p. m. — Boat Cruise and Buffet Dinner

There will be a "Twilight Cruise" on beautiful Biscayne Bay with buffet dinner on board.

Saturday, June 11

6:00 p. m. — College Convocation
7:00 p. m. — Cocktail Party
(sponsored by the Florida Chapter of the College)
7:30 p. m. — Annual Presidents' Banquet
9:00 p. m. — After-Dinner Dancing
The above functions will be held at the Saxony Hotel.

Sunday, June 12

12:00 noon — Brunch and Fashion Show
Fleur-de-lis Room
Fontainebleau Hotel
Beautiful surroundings — delicious brunch — and Fashions of the Hour.

TECHNICAL EXHIBITORS

Barnes-Hind Pasna Company
Sunnyvale, California

Brewer Laboratories
Worcester, Massachusetts

Warren E. Collins, Inc.
Boston, Massachusetts

Corco, Inc.
Culver City, California

Darwin Laboratories
Los Angeles, California

Lester A. Dine Company
Long Island City, New York

Dumas-Wilson & Company
St. Louis, Missouri

J. H. Emerson Company
Cambridge, Massachusetts

E. Fougera and Company, Inc.
Hicksville, New York

Great Books of the Western World
Grand Rapids, Michigan

Grune & Stratton, Inc.
New York, New York

Instrumentation Associates
New York, New York

Lederle Laboratories
Pearl River, New York

Eli Lilly Company
Indianapolis, Indiana

Linde Company
New York, New York

Thomas J. Mahon, Inc.
Englewood Cliffs, New Jersey

Medtronic, Inc.
Minneapolis, Minnesota

Melchior, Armstrong & Dessau
Ridgefield, New Jersey

Merck, Sharp and Dohme
Philadelphia, Pennsylvania

Micro X-ray Recorder, Inc.
Chicago, Illinois

Miles Reproducer Comp.
New York, New York

Mine Safety Appliances Company
Pittsburgh, Pennsylvania

Mist O_2 Gen Equipment Company
Oakland, California

J. J. Monaghan Company
Denver, Colorado

National Cylinder Gas Company
Chicago, Illinois

North American Philips Company
New York, New York

Ohio Chemical & Surgical Equipment Co.
Madison, Wisconsin

Orthopedic Frame Company
Kalamazoo, Michigan

Oxygen Equipment Manufacturing Co.
East Norwalk, Connecticut

The Panray Corp.
Englewood, New Jersey

George P. Pilling & Son Company
Philadelphia, Pennsylvania

Puritan Compressed Gas Corporation
Kansas City, Missouri

Sanborn Company
Waltham, Massachusetts

G. D. Searle & Company
Chicago, Illinois

Sherman Laboratories
Detroit, Michigan

Spinco Division, Beckman Instruments
Palo Alto, California

Thompson Engineering Products
Boulder, Colorado

U. S. Vitamin and Pharmaceutical Corp.
New York, New York

Winthrop Laboratories
New York, New York

Yaponefrin Company,
New York, New York

109th ANNUAL MEETING

AMERICAN MEDICAL ASSOCIATION

June 13-17, 1960, Miami Beach

Be sure to register for the Section on Diseases of the Chest

Arrangements have been made for College members to register for the American Medical Association meeting at the Saxony Hotel on Sunday, June 12.

HOTEL RESERVATION FORM

26th Annual Meeting
AMERICAN COLLEGE OF CHEST PHYSICIANS
June 8 - 12, 1960, Miami Beach, Florida

Annual Meeting
AMERICAN MEDICAL ASSOCIATION
June 13 - 17, 1960, Miami Beach

The Saxony Hotel, Miami Beach, will be headquarters for the 26th Annual Meeting of the American College of Chest Physicians; however, there is no hotel in Miami Beach large enough to house all of the members of the College attending the annual meeting. Seven excellent hotels within walking distance of the Saxony Hotel, which is located on the oceanfront from 32nd to 33rd Streets, have set aside rooms for College members. All of the hotels are completely air-conditioned, and have swimming pools and private beaches.

Please complete this reservation form and return it to the College offices as soon as possible. Reservations will be accepted in the order received and confirmations will be forwarded directly from the hotel. It would be helpful if first, second and third choices are indicated.

Members who plan to attend the meeting of the American Medical Association may remain in their hotels for both meetings. Please be sure to indicate arrival and departure dates.

Arrangements have been made for College members to register in advance for the American Medical Association meeting and those registered may pick up their badges and programs at the Saxony Hotel on Sunday, June 12.

Please complete and return this form at once

TO: American College of Chest Physicians
112 East Chestnut Street, Chicago 11, Illinois

FROM: _____
(name)
Address _____

City/State _____

Accompanied by _____

Arrival Date _____ Departure Date _____

Remarks _____
Please indicate 1st, 2nd and 3rd choices by number

CIRCLE RATE DESIRED

Choice No.		Single or Double Western Exposure	Single or Double Oceanfront or Oceanview
_____	ALGIERS HOTEL Oceanfront, 25th to 26th Sts.	$12.00 - 14.00	$14.00 - 16.00
_____	CADILLAC HOTEL Oceanfront, 39th to 40th Sts.	$12.00 - 14.00	$12.00 - 14.00
_____	CARIBBEAN HOTEL Oceanfront, 37th to 38th Sts.	$10.00 - 12.00	$12.00 - 14.00
_____	PRESIDENT MADISON HOTEL Oceanfront, 38th to 39th Sts.	$10.00 - 12.00	$12.00 - 14.00
_____	SANS SOUCI HOTEL Oceanfront, 31st to 32nd Sts.	$12.00 - 14.00 - 16.00	$18.00
_____	SEA ISLE HOTEL Oceanfront, 30th to 31st Sts.	$12.00 - 14.00	$14.00 - 16.00
_____	SEVILLE HOTEL Oceanfront, 29th to 30th Sts.	$12.00 - 14.00	$14.00 - 16.00

Third person in room, $3-4 extra daily. Fourth person in room $2-3 extra daily. Some suites are available at additional room charge for parlor. Will you accept a room with western exposure if oceanfront or oceanview rooms are not available? Yes_____ No_____

ADVANCE REGISTRATION

There is no registration fee for members

The registration fee for non-members is $25.00

(FEE INCLUDES ATTENDANCE AT THE POSTGRADUATE SEMINARS)

By completing this form and returning it at once to the Executive Offices of the College, you will avoid having to stand in line at the Registration Desk at the annual meeting in Miami Beach. Your badge and program, as well as luncheon, banquet and seminar tickets, will be prepared in advance and will be awaiting your arrival at the Saxony Hotel. Please complete both sides of the Advance Registration Form and mail promptly. Thank you.

Non-members must enclose a registration fee of $25 with this form. Please make check payable to the **American College of Chest Physicians.**

Return the form to: American College of Chest Physicians
112 East Chestnut Street
Chicago 11, Illinois

FOR HOTEL RESERVATIONS, PLEASE COMPLETE FORM ON OPPOSITE PAGE

Advance Registration Form

_____Member _____Non-member

Please Print

Name_____

Address_____

City and State_____

Accompanied by_____

Hotel_____Arrival date_____Departure_____

PLEASE REGISTER ME FOR THE AMA MEETING_____

Reservation Form—Annual Presidents' Banquet

Saturday, June 11, 1960 — Cocktails — Dinner — Dancing
Saxony Hotel, Miami Beach — **Tickets: $9.75 each**

I wish to reserve_____tickets for the Annual Presidents' Banquet, Saturday, June 11, 7:30 p. m. (price includes cocktails, dinner and dancing).

ALL SEATS RESERVED

RESERVATION FORM

Annual Presidents' Banquet

All places at the Annual Presidents' Banquet are reserved. Tables will be assigned in order requests are received. Please order your tickets at once so that you may be assigned your table early. Tables for ten may be reserved upon receipt of payment of tickets and names of persons in the party. A banquet reservation form may be found on the reverse side of this page.

Postgraduate Seminars

The program of postgraduate seminars appears on pages 460 and 461 of this issue of the journal. There is a tuition fee of $7.50 for each seminar. Registration for the postgraduate seminars is limited and reservations will be accepted in the order received. Please use the reservation form on this page and submit promptly to the Executive Offices of the College.

Round Table Luncheons

Round table luncheon discussions will be held on Friday, Saturday and Sunday, June 10, 11 and 12. The program of subjects may be found on pages 474, 475 and 476 of this journal. As tickets for the round table discussions are usually sold out in advance of the meeting, members are urged to make their reservations at once. Please submit the reservation form at the bottom of this page.

Postgraduate Seminars, Wednesday, June 8

$7.50 each for members
Included in $25.00 registration fee for non-members

Morning Sessions (9 a.m. - 12 noon)		**Afternoon Sessions (2:00 - 5:00 p.m.)**	
First choice	A. M._____	First choice	P. M._____
Second choice	A. M._____	Second choice	P. M._____

Please indicate choice by number as listed in program.

Round Table Luncheons

Tickets: $4.00 each

	Friday, June 10	**Saturday, June 11**	**Sunday, June 12**
First choice	A-_____	B-_____	C-_____
Second choice	A-_____	B-_____	C-_____
Third choice	A-_____	B-_____	C-_____

Please indicate choice by number as listed in program.

I am enclosing my check in the amount of $_____for reservations as indicated on this form.

Please make checks payable to American College of Chest Physicians.